IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BOSTON SCIENTIFIC CORPORATION and BOSTON SCIENTIFIC SCIMED, INC., Plaintiffs/Counter-Defendants, v. JOHNSON & JOHNSON, CORDIS CORPORATION, and WYETH Defendants/ Counter-Plaintiffs.	**REDACTED PUBLIC VERSION** Civil Action No. 07-333-SLR Civil Action No. 07-348-SLR Civil Action No. 07-409-SLR
BOSTON SCIENTIFIC CORPORATION and BOSTON SCIENTIFIC SCIMED, INC., Plaintiffs/Counter-Defendants, v. JOHNSON & JOHNSON, CORDIS CORPORATION, and WYETH Defendants/Counter-Plaintiffs.	Civil Action No. 07-765-SLR

APPENDIX OF EXHIBITS TO DEFENDANTS/COUNTER-PLAINTIFFS JOHNSON & JOHNSON AND CORDIS CORPORATION'S OPPOSITION TO PLAINTIFFS' MOTIONS FOR SUMMARY JUDGMENT OF NON-INFRINGEMENT

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Schuler et al.

(10) **Patent No.: US 6,384,046 B1**
(45) **Date of Patent: May 7, 2002**

(54) **USE OF 40-O-(2-HYDROXY) ETHYLRAPANYCIN FOR TREATMENT OF RESTENOSIS AND OTHER DISORDERS**

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(30) **Foreign Application Priority Data**

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(58) **Field of Search** 514/291

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(57) **ABSTRACT**

This invention relates to the use of 40-O-(2-hydroxy)ethyl-rapamycin for the prevention or treatment of neointimal proliferation and thickening, restenosis, and vascular occlusion following vascular injury.

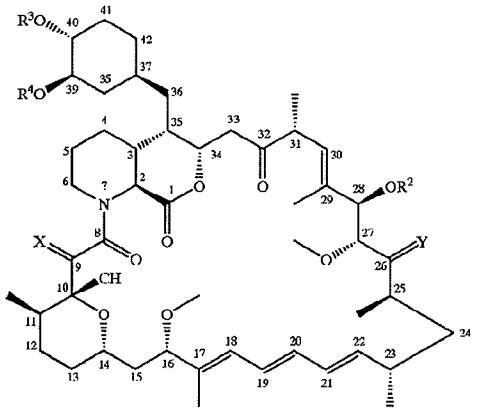
4 Claims, No Drawings

USE OF 40-O-(2-HYDROXY) ETHYLRAPANYCIN FOR TREATMENT OF RESTENOSIS AND OTHER DISORDERS

This application is a continuation of Ser. No. 09/155,210, filed Sep. 23, 1998, now abandoned, which is a 371 of PCT/EP97/01548, filed Mar. 26, 1997.

The present invention relates to a new use, in particular a new use for a compound group comprising derivatives of rapamycin, in free form or in pharmaceutically acceptable salt or complex form. Suitable derivatives of rapamycin include e.g. compounds of formula I

(I)



wherein

X is (H,H) or O;

Y is (H,OH) or O;

R^1 and R^2 are independently selected from

H,. alkyl, arylalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkoxycarbonylalkyl, hydroxyalkylarylalkyl, dihydroxyalkylarylalkyl, acyloxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxycarbonylaminoalkyl, acylaminoalkyl, arylsulfonamidoalkyl, allyl, dihydroxyalkylallyl, dioxolanylallyl, dialkyl-dioxolanylalkyl, di(alkoxycarbonyl)-triazolyl-alkyl and hydroxy-alkoxy-alkyl; wherein "alk-" or "alkyl" is C_{1-6}alkyl, branched or linear; "aryl" is phenyl or tolyl; and acyl is a radical derived from a carboxylic acid; and

R^4 is methyl or

R^4 and R^1 together form C_{2-6}alkyl;

provided that R^1 and R^2 are not both H; and hydroxyalkoxy-alkyl is other than hydroxyalkoxymethyl.

Such compounds are disclosed in WO 94/09010 the contents of which, in particular with respect to the compounds, are incorporated herein by reference.

Acyl as may be present in R_1 or R_2, is preferably R_aCO— wherein R_a is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl, aryl, aryl C_{1-6}alkyl (wherein aryl is as defined above) or heteroaryl, e.g. a residue derived from a 5 or 6 membered heterocycle comprising N, S or O as a heteroatom and optionally one or two N as further heteroatoms. Suitable heteroaryl include e.g. pyridyl, morpholino, piperazinyl and imidazolyl.

Examples of such compounds include:

1. 40-O-Benzyl-rapamycin
2. 40-O-(4'-Hydroxymethyl)benzyl-rapamycin
3. 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin
4. 40-O-Allyl-rapamycin
5. 40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin
6. (2'E,4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl)-rapamycin
7. 40-O-(2-Hydroxy)ethoxycarbonylmethyl-rapamycin
8. 40-O-(2-Hydroxy)ethyl-rapamycin
9. 40-O-(3-Hydroxy)propyl-rapamycin
10. 40-O-(6-Hydroxy)hexyl-rapamycin
11. 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin
12. 40-O-[(3S)-2,2-Dimethyldioxolan-3-yl]methyl-rapamycin
13. 40-O-[(2S)-2,3-Dihydroxyprop-1-yl]-rapamycin
14. 40-O-(2-Acetoxy)ethyl-rapamycin
15. 40-O-(2-Nicotinoyloxy)ethyl-rapamycin
16. 40-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin
17. 40-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin
18. 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin
19. 39-O-Desmethyl-39,40-O,O-ethylene-rapamycin
20. (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin
21. 28-O-Methyl-rapamycin
22. 40-O-(2-Aminoethyl)-rapamycin
23. 40-O-(2-Acetaminoethyl)-rapamycin
24. 40-O-(2-Nicotinamidoethyl)-rapamycin
25. 40-O-(2-(N-Methyl-imidazo-2'-ylcarboxamido)ethyl)-rapamycin
26. 40-O-(2-Ethoxycarbonylaminoethyl)-rapamycin
27. 40-O-(2-Tolylsulfonamidoethyl)-rapamycin
28. 40-O-[2-(4',5'-Dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin

A preferred compound is e.g. 40-O-(2-hydroxy)ethyl-rapamycin (referred thereafter as Compound A).

Compounds of formula I have, on the basis of observed activity, e.g. binding to macrophilin-12 (also known as FK-506 binding protein or FKBP-12), e.g. as described in WO 94/09010, been found to be useful e.g. as immunosuppressants, e.g. in the treatment of acute allograft rejection.

Organ transplants of liver, kidney, lung and heart are now regularly performed as treatment for endstage organ disease. Because of the current shortage of human donors for transplantable allografts, attention has focused on the possibility of using xenografts (transplants between species) in transplantation. One of the major obstacles in transplanting successfully xenografts in humans is immunological.

A further obstacle in allo- and xenotransplantation is the chronic rejection and thus organ transplantation is not yet a clinically viable solution to irreversible organ disease.

Chronic rejection, which manifests as progressive and irreversible graft dysfunction, is the leading cause of organ transplant loss, in some cases already after the first postoperative year. The clinical problem of chronic rejection is clear from transplantation survival times; about half of kidney allografts are lost within 5 years after transplantation, and a similar value is observed in patients with heart allografts.

Chronic rejection is considered as a multifactorial process in which not only the immune reaction towards the graft but also the response of the blood vessel walls in the grafted organ to injury ("response-to-injury" reaction) plays a role.

The variant of chronic rejection with the worst prognosis is an arteriosclerosis-like alteration, also called transplant vasculopathy, graft vessel disease, graft arteriosclerosis, transplant coronary disease, etc. This vascular lesion is characterized by migration and proliferation of smooth muscle cells, probably under influence of growth factors that are amongst others synthesized by endothelial cells. This leads to intimal proliferation and thickening, smooth muscle cell hypertrophy repair, and finally to gradual luminal obliteration (vascular remodelling). It appears to progress also through repetitive endothelial injury induced amongst others by host antibody or antigen-antibody complexes; also so-called non-immunological factors like hypertension, hyperlipidemia, hypercholesterolemia etc. play a role.

Chronic rejection appears to be inexorable and uncontrollable because there is no known effective treatment or prevention modality. Thus, there continues to exist a need for a treatment effective in preventing, controlling or reversing manifestations of chronic graft vessel diseases.

There also continues to exist a need to prevent or treat restenosis or vascular occlusions as a consequence of proliferation and migration of intimal smooth muscle cell, e.g. induced by vascular surgeries such as angioplasty.

In accordance with the present invention, it has now surprisingly been found that compounds of formula I inhibit vasculopathies such as vascular remodelling and are particularly indicated to prevent or combat chronic rejection in a transplanted organ.

In accordance with the particular findings of the present invention, there is provided:

1. A method for preventing or treating neointimal proliferation and thickening in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound of formula I.

In a series of further specific or alternative embodiments, the present invention also provides:

2.1. A method for preventing or combating manifestations of chronic rejection in a recipient of organ or tissue transplant comprising the step of administering to said recipient a therapeutically effective amount of a compound of formula I.

2.2 A method for preventing or combating graft vessel diseases, e.g. transplant vasculopathies, arteriosclerosis or atherosclerosis, in a recipient of organ or tissue transplant, comprising the step of administering to said recipient a therapeutically effective amount of a compound of formula I.

By manifestations of chronic rejection are meant the conditions resulting from the immune reaction towards the graft and the response of the blood vessel walls in the grafted organ or tissue as indicated above. Compounds of formula I are useful for reducing chronic rejection manifestations or for ameliorating the conditions resulting from chronic rejection.

The organ or tissue transplantation may be performed from a donor to a recipient of a same or different species. Among such transplanted organs or tissues and given illustratively are heart, liver, kidney, spleen, lung, small bowel, and pancreas, or a combination of any of the foregoing.

In a further or alternative embodiment the invention provides:

3. A method for preventing or treating intimal smooth muscle cell proliferation and migration, e.g. restenosis, and/or vascular occlusion following vascular injury, e.g. angioplasty, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound of formula I.

In a further or alternative embodiment, the present invention also provides:

4. A method for preventing or combating acute or chronic rejection in a recipient of organ or tissue xenograft transplant comprising administering to said recipient a therapeutically effective amount of a compound of formula I.

Xenograft organ or tissue transplants include e.g. heart, liver, kidney, spleen, lung, small bowel, pancreatic (complete or partial, e.g. Langerhans islets), skin and bone marrow xenografts.

As alternative to the above the present invention also provides:

5. A compound of formula I for use in any method as defined under 1 to 4 above; or

6. A compound of formula I for use in the preparation of a pharmaceutical composition for use in any method as defined under 1 to 4 above; or

7. A pharmaceutical composition for use in any method as defined under 1 to 4 above comprising a compound of formula I together with one or more pharmaceutically acceptable diluents or carriers therefor.

Utility of the compounds of formula I in treating diseases and conditions as hereinabove specified, may be demonstrated in animal tests, for example in accordance with the methods hereinafter described.

A. Chronic Allograft Rejection

The kidney of a male DA ($RT1^a$) rat is orthotopically transplanted into a male Lewis ($RT1^1$) recipient. In total 24 animals are transplanted. All animals are treated with cyclosporine A at 7.5 mg/kg/day per os for 14 days starting on the day of transplantation, to prevent acute cellular rejection. Contralateral nephrectomy is not performed. Each experimental group treated with a distinct dose of a compound of formula I or placebo comprises six animals.

Starting at day 53–64 after transplantation, the recipient animals are treated per os for another 69–72 days with a compound of formula I or receive placebo. At 14 days after transplantation animals are subjected to graft assessment by magnetic resonance imaging (MRI) with perfusion measurement of the kidneys (with comparison of the grafted kidney and the own contralateral kidney). This is repeated at days 53–64 after transplantation and at the end of the experiment. The animals are then autopsied. Rejection parameters such as MRI score, relative perfusion rate of the grafted kidney and histologic score of the kidney allograft for cellular rejection and vessel changes are determined and statistically analyzed. Administration of a compound of formula I, e.g. Compound A, at a dose of 0.5 to 2.5 mg/kg in this rat kidney allograft model yields a reduction in all above mentioned rejection parameters. In this assay, animals treated per os with 2.5 mg/kg/day of Compound A have a significantly lower MRI score of rejection, histologic score for cellular rejection and vessel changes and a significantly lower reduction in perfusion rate assessed by MRI than the animals of the placebo group.

B. Aorta Transplantation

In this model of aorta transplantation in the rat, an allogeneic response to the graft does not destroy the graft, but it evokes pathological changes resembling those of chronic rejection in clinical transplantation. These include infiltration into the adventitia of mononuclear cells (lymphocytes, macrophages, some plasma cells), and thickening of the intima.

Donor aorta between the branch of the renal artery and the start of the caudal mesenteric aorta, about 1 cm in length, is harvested from a male DA ($RT1^a$) rat and transplanted

orthotopically in a male Lewis (RT1[1]) rat. Weekly after transplantation, the body weight is recorded. At autopsy, the graft with part of the aorta of the recipient just above and below the transplant is removed. It is perfused ex vivo with phosphate-buffered saline supplemented with 2% paraformaldehyde and 2.5% glutaraldehyde for about 2 minutes, then for 24 hours fixed by immersion fixation in the same solution, and thereafter fixed in 4% buffered formalin. Pieces of the graft are embedded in paraffin, in such a way that both a transversal section and a longitudinal section is made of the grafted aorta and the recipient's own aorta.

Sections of 4 μm thickness are stained by hematoxylin-eosin, elastica-von-Gieson and periodic-acid-Schiff. Apart from conventional light microscopy, images are recorded by confocal laser scanning microscopy. From each section, four areas are scanned, and from each area the thickness of the intima and intima+media is measured at five locations.

At autopsy, weight and histology is performed for thymus, spleen, liver, kidney, testes and seminal vesicles.

A first experiment includes 4 groups, each comprising 4 animals. In one group isogeneic transplantations (Lewis to Lewis) are performed, and animals receive a placebo microemulsion, the other groups comprise allogeneic transplantations, and animals receive per os either placebo microemulsion or a compound of formula I in microemulsion at 2.5 mg/kg/day. The experiment is terminated at 7 weeks after transplantation.

A second experiment includes 4 groups, each comprising 4 animals. In all cases allogeneic transplants are performed, and animals receive per os either placebo microemulsion or a compound of formula I in microemulsion at 0.63, 1.25, 2.5 or 5.0 mg/kg/day. The experiment is terminated 11 weeks after transplantation.

In both experiments, the compounds of formula I, particularly Compound A significantly inhibit graft infiltration and neointima formation.

C. Angioplasty

Studies on anioplasty are done in the model of balloon catheter injury: Balloon catheterization is performed on day 0, essentially as described by Powell et al. (1989). Under Isofluorane anaesthesia, a Fogarty 2F catheter is introduced into the left common carotid artery via the external carotid and inflated (distension≈10 μl H2O). The inflated balloon is withdrawn along the length of the common carotid three times, the latter two times whilst twisting gently to obtain a uniform de-endothelialization. The cathether is then removed, a ligature placed around the external carotid to prevent bleeding and the animals allowed to recover.

2 groups of 12 RoRo rats (400 g, approximately 24 weeks old) are used for the study: one control group and one group receiving the compound of formula I. The rats are fully randomized during all handling, experimental procedures and analysis.

The compound to be tested is administered p.o. (gavage) starting 3 days before balloon injury (day −3) until the end of the study, 14 days after balloon injury (day +14). Rats are kept in individual cages and allowed food and water ad libidum.

The rats are then anaesthetized with Isofluorane, a perfusion catheter inserted through the left ventricle and secured in the aortic arch, and an aspiration cannula inserted into the right ventricle. Animals are perfused under a perfusion pressure of 150 mmHg, firstly for 1 min. with 0.1 M phosphate buffered saline solution (PBS, pH 7.4) and then for 15 min. with 2.5 % glutaraldehyde in phosphate buffer (pH 7.4). The perfusion pressure is 150 mmHg at the tip of the cannula (≈100 mmHg in the carotid artery), as determined in a preliminary experiment by introducing a cannula attached to a pressure transducer into the external carotid). Carotid arteries are then excised, separated from surrounding tissue and immersed in 0.1 M cacodylate buffer (pH 7.4) containing 7% saccharose and incubated overnight at 4° C. The following day the carotids are immersed and shaken for 1 h at room temperature in 0.05% KMnO4 in 0.1 M cacodylate. The tissues are then dehydrated in a graded ethanol series; 2×10 min in 75%,2×10 min in 85%, 3×10 min in 95% and 3×10 min in 100% ethanol. The dehydrated carotids are then embedded in Technovit 7100 according to the manufacturers recommendation. The embedding medium is left to polymerize overnight in an exsiccator under argon, since oxygen is found to inhibit proper hardening of the blocks.

Sections 1–2 μm thick are cut from the middle section of each carotid with a hard metal knife on a rotary microtome and stained for 2 min with Giemsa stain. About 5 sections from each carotid are thus prepared and the cross-sectional area of the media, neointima and the lumen morphometrically evaluated by means of an image analysis system (MCID, Toronto, Canada).

In this assay, the compounds of formula I inhibit myointimal proliferation when administered per os at a daily dose of from 0.5 to 2.5 mg/kg. Intimal thickening is significantly less in the vessels of the rats that receive Compound A compared to the control animals, e.g. at 0.5 mg/kg statistical inhibition of neointima formation of 50%, at 2.5 mg/kg significant inhibition of 75%.

D. In vivo Heart Xenotransplantation (Hamster-to-rat)

The hamster-into-rat xenograft combination is a so-called difficult concordant combination. Rats do not have natural anti-hamster antibody in sufficient amounts to yield immediate hyperacute rejection as observed in concordant combinations; however, rejection in untreated recipients occurs within 3–4 days, by antibodies in combination with complement. This is visualized in histology by destruction of blood vessels, exsudation and extravasation of erythrocytes, and influx by polymorpho-nuclear granulocytes; often there are signs of hemorrhage and thrombosis. Once this rejection has been overcome by effective inhibition of antibody synthesis or complement inactivation, a cellular rejection can emerge later on. This is visualized in histology by influx of mononuclear cells, including lymphocytes, lymphoblastoid cells, and macrophages, and destruction of the myocyte parenchyma. The inhibition of cellular rejection requires more immuno-suppression than that of allografts. Congenitally athymic (rnu/rnu) rats lack a competent (thymus-dependent) cellular immune system and generally are unable to reject allografts. Such animals do reject a hamster xenograft within 3–4 days in a similar fashion as euthymic rats, indicative that (at least part of) anti-hamster antibody synthesis in rats occurs following a thymus-independent B-cell response. Such recipients are useful in hamster xenografting to evaluate rejection by thymus-independent antibody-mediated rejection.

The heart of a Syrian hamster is heterotopically transplanted in the abdomen of a male Lewis (RT1[1]) rat with anastomoses between the donor and recipient's aorta and the donor right pulmonary artery to the recipient's inferior vena cava. The graft is monitored daily by palpation of the abdomen. Rejection is concluded in case of cessation of heart beat. Animals are weighed weekly. In the present series of experiments, the endpoint is set to 28 days. Animals are subjected to autopsy; apart from the graft, weight and histoloy is assessed for thymus, spleen, liver, seminal vesicles and testes. Blood is taken and processed to serum

for the determination of cytolytic anti-hamster erythrocyte antibody and hemolytic complement activity.

In this assay, compounds of formula I, e.g. Compound A, result in prolonged graft survival, in both athymic and euthymic recipients.

Daily dosages required in practicing the method of the present invention will vary depending upon, for example, the compound of formula I employed, the host, the mode of administration and the severity of the condition to be treated. A preferred daily dosage range is about from 0.25 to 25 mg as a single dose or in divided doses.

Suitable daily dosages for patients are on the order of from e.g. 0.2 to 25 mg p.o. preferably 5 to 25. The compounds of formula I may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets, capsules, drink solutions, nasally, pulmonary (by inhalation) or parenterally, e.g. in the form of injectable solutions or suspensions. Suitable unit dosage forms for oral administration comprise from ca. 0.05 to 12.5 mg, usually 1 to 10 mg active ingredient, e.g. Compound A, together with one or more pharmaceutically acceptable diluents or carriers therefor.

When used to prevent or treat chronic rejection or xenotransplant rejection as hereinabove specified the compounds of formula I may be administered as the sole active ingredient or together with other drugs in immunomodulating regimens. For example, the compounds of formula I may be used in combination with cyclosporins or ascomycins, or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, etc.; cortieosteroids; cyclophosphamide; azathioprene; methotrexate; brequinar; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine, immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, or CD58 or their ligands; or other immunomodulatory compounds, e.g. CTLA41 g.

Where the compounds of formula I are administered in conjunction with other immunosuppressive/immunomodulatory, therapy, e.g. for preventing or treating chronic rejection or xenotransplant rejection as hereinabove specified, dosages of the co-administered immunosuppressant or immuno-modulatory compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a cyclosporin, on the specific drug employed, on the condition being treated, and so forth. In accordance with the foregoing the present invention provides in a yet further aspect:

8. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of formula I and a second drug substance, said second drug substance being an immunosuppressant or immunomodulatory drug, e.g. as indicated above.

FORMULATION EXAMPLE

Capsules

Ethanol	20.0 mg
1,2-propylene glycol	81.0 mg
Refined oil	121.5 mg
Cremophor RH40	202.5 mg
Compound A	20.0 mg
Total	500 mg

Compounds of formula I are well tolerated at dosages required for use in accordance with the present invention. For example, the NTEL for Compound A in a 4-week toxicity study is 0.5 mg/kg/day in rats and 1.5 mg/kg/day in monkeys.

What is claimed is:

1. A method for preventing or treating:

neointimal proliferation and thickening and/or restenosis and/or vascular occlusion following vascular injury comprising administering to a subject in need thereof an effective amount of 40-O-(2-hydroxy)ethyl-rapamycin.

2. A method according to claim 1 for preventing or treating neointimal proliferation and thickening.

3. A method according to claim 1 for preventing or treating restenosis and/or vascular occlusion following vascular injury.

4. A method according to claim 1 for preventing or treating vascular occlusion following vascular injury.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,384,046 B1
DATED : May 7, 2002
INVENTOR(S) : Schuler et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [54], should read: -- **USE OF 40-O-(2-HYDROXY)ETHYLRAPAMYCIN FOR TREATMENT OF RESTENOSIS AND OTHER DISORDERS** --.

Signed and Sealed this

Twenty-second Day of October, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US006440990B1

(12) **United States Patent**
Cottens et al.

(10) **Patent No.: US 6,440,990 B1**
(45) **Date of Patent: *Aug. 27, 2002**

(54) **O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS**

(75) Inventors: **Sylvain Cottens**, Witterswil; **Richard Sedrani**, Basel, both of (CH)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **08/862,911**

(22) Filed: **May 23, 1997**

Related U.S. Application Data

(62) Division of application No. 08/416,673, filed as application No. PCT/EP93/02604 on Sep. 24, 1993, now Pat. No. 5,665,772.

(30) **Foreign Application Priority Data**

Oct. 9, 1992 (GB) 9221220

(51) **Int. Cl.**[7] **A61K 31/436**; C07D 491/10

(52) **U.S. Cl.** **514/291**; 540/456

(58) **Field of Search** 540/456; 514/291

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(57) **ABSTRACT**

Novel derivatives of rapamycin, particularly 9-deoxo-rapamycins, 26-dihydro-rapamycins, and 40-O-substituted and 28,40-O,O-disubstituted rapamycins. are found to have pharmaceutical utility, particularly as immunosuppressants.

35 Claims, No Drawings

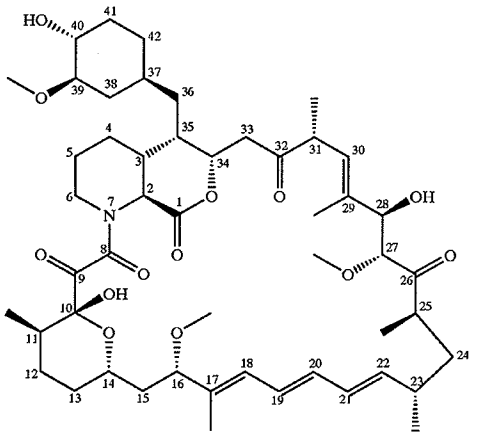
O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS

This is a division of application Ser. No. 08/416,673, filed Apr. 7, 1995 and now U.S. Pat. No. 5,665,772, which is a 371 of International Application No. PCT/EP93/02604, filed Sep. 24, 1993.

This invention comprises novel alkylated derivatives of rapamycin having pharmaceutical utility especially as immunosuppressants.

Rapamycin is a known macrolide antibiotic produced by *Streptomvces hyngroscopicus* having the structure depicted in Formula A:

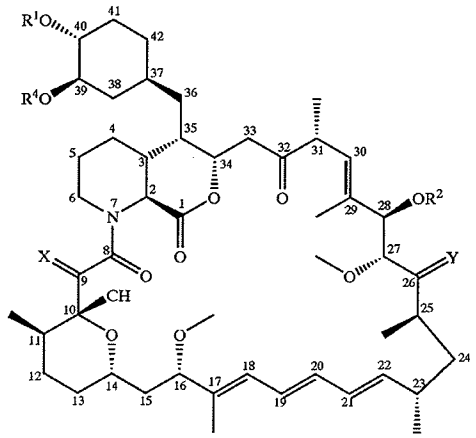
(A)



See. e.g.. McAlpine. J. B., et al., J. Antibiotics (1991) 44: 688; Schreiber. S. L., et al., J. Am. Chem. Soc. (1991) 113: 7433; U.S. Pat. No. 3,929,992. Rapamycin is an extremely potent immunosuppressant and has also been shown to have antitumor and antifungal activity. Its utility as a pharmaceutical, however, is restricted by its very low and variable bioavailability as well as its high toxicity. Moreover, rapamycin is highly insoluble, making it difficult to formulate stable galenic compositions.

It has now surprisingly been discovered that certain novel derivatives of rapamycin (the Novel Compounds) have an improved pharmacologic profile over rapamycin, exhibit greater stability and bioavailability, and allow for greater ease in producing galenic formulations. The Novel Compounds are alkylated derivatives of rapamycin having the structure of Formula I:

(I)



wherein

X is (H,H) or O;

Y is (H,OH) or O;

R^1 and R^2 are independent selected from

H, alkyl, thioalkyl, arylalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkylarylalkyl, dihydroxyalkylaryalkyl, alkoxyalkyl, acyloxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxycarbonylaminoalkyl, acylaminoalkyl, arylsulfonamidoalkyl, allyl, dihydroxyalkylallyl, dioxolanylallyl, carbalkoxyalkyl, and $(R^3)_3Si$ where each R^3 is independenty selected from H, methyl, ethyl, isopropyl, t-butyl, and phenyl; wherin "alkl-" or "alky-" refers to C_{1-6} alkyl branched or linear preferably C_{1-3} alkyl, in which the carbon chain may be optionally interrupted by an ether (-O-) linkage; and

R^4 is methyl or R^4 and R^1 together form C_{2-5} alkylene;

provided that R^1 and R^2 are not both H; and

provided that where R^1 is $(R^3)_3Si$ or carbalkoxyalkyl, X and Y are not both O.

Preferred Novel Compounds include the following:

1. 40-O-Benzyl-rapamycin
2. 40-O -(4'-Hydroxymethyl)benzyl-rapamycin
3. 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin
4. 40-O-Allyl-rapamycin
5. 40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin
6. (2'E, 4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl)-rapamycin
7. 40-O-(2-Hydroxy)ethoxycarbonylmethyl-rapamycin
8. 40-O-(2-Hydroxy)ethyl-rapamycin
9. 40-O-(3-Hydroxy)propyl-rapamycin
10. 40-O-(6-Hydroxy)hexyl-rapamycin
11. 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin
12. 40-O-[(3S)-2,2-Dimethyldioxolan-3-yl]methyl-rapamycin

13. 40-O-[(2S)-2,3-Dihydroxyprop-1-yl]-rapamycin
14. 40-O-(2-Acetoxy)ethyl-rapamycin
15. 40-O-(2-Nicotinoyloxy)ethyl-rapamycin
16. 40-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin
17. 40-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin
18. 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin
19. 39-O-Desmethyl-39,40-O,O-ethylene-rapamycin
20. (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin
21. 28-O-Methyl-rapamycin
22. 40-O-(2-Aminoethyl)-rapamycin
23. 40-O-(2-Acetaminoethyl)-rapamycin
24. 40-O-(2-Nicotinamidoethyl)-rapamycin
25. 40-O-(2-(N-Methyl-imidazo-2'-ylcarbethoxamido) ethyl)-rapamycin
26. 40-O-(2-Ethoxycarbonylaminoethyl)-rapamycin
27. 40-(2-Tolylsulfonamidoethyl)-rapamycin
28. 40-O-[2-(4',5'-Dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin

The Novel Compounds for immunosuppressive use are preferably the 40-O-substituted rapamycins where X and Y are both O, R^2 is H, R^4 is methyl, and R^1 is other than H; most preferably where R^1 is selected from hydroxyalkyl, hydroxyalkoxyalkyl, acylaminoalkyl, and aminoalkyl; especially 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy) propyl-rapamycin. 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-O-(2-acetaminoethyl)-rapamycin).

Preferably, O-substitution at C40 or O,O-disubstitution at C28 and C40 is performed according to the following general process: Rapamycin (or dihydro or deoxorapamycin) is reacted with an organic radical attached to a leaving group (e.g., RX where R is the organic radical, e.g., an alkyl, allyl, or benzyl moiety, which is desired as the O-substituent, and X is the leaving group, e.g., CCl_3C (NH)O or CF_3SO_3) under suitable reaction conditions, preferably acidic or neutral conditions, e.g., in the presence of an acid like trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their respective pyridinium or substituted pyridinium salts when X is $CCl_3C(NH)O$ or in the presence of a base like pyridine, a substituted pyridine, diisopropylethylamine or pentamethylpiperidine when X is CF_3SO_3. O-substitutions at C28 only are accomplished in the same manner but with prior protection at C40. Further modifications are possible. For example, where the substituent is allyl, the isolated monosubstituted double bond of the allyl moiety is highly amenable to further modification.

The 9-deoxorapamycin compounds are preferably produced by reducing a rapamycin using hydrogen sulfide, by reacting rapamycin with diphenyldiselenide and tributylphosphine or by other suitable reduction reaction.

The 26-dihydro-rapamycins are preferably produced by reducing rapamycins or 9-deoxorapamycins from keto to hydroxy at C26 by a mild reduction reaction, such as a borohydride reduction reaction.

The Novel Compounds are particularly useful for the following conditions:

a) Treatment and prevention of organ or tissue transplant rejection, e.g. for the treatment of recipients of e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants. They are also indicated for the prevention of graft-versus-host disease, such as following bone marrow transplantation.

b) Treatment and prevention of autoimmune disease and of inflammatory conditions in particular inflammatory

conditions with an etiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific autoimmune diseases for which the compounds of the invention may be employed include, autoimmune hematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease) endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy) and juvenile dermatomyositis.

c) Treatment and prevention of asthma.

d) Treatment of multi-drug resistance (MDR). The Novel Compounds suppress P-glycoproteins (Pgp), which are the membrane transport molecules associated with MDR. MDR is particularly problematic in cancer patients and AIDS patients who will not respond to conventional chemotherapy because the medication is pumped out of the cells by Pgp. The Novel Compounds are therefore useful for enhancing the efficacy of other chemotherapeutic agents in the treatment and control of multidrug resistant conditions such as multidrug resistant cancer or multidrug resistant AIDS.

e) Treatment of proliferative disorders, e.g. rumors, hyperproliferative skin disorder and the like.

f) Treatment of fungal infections.

g) Treatment and prevention of inflammation, especially in potentiating the action of steroids.

h) Treatment and prevention of infection, especially infection by pathogens having Mip or Mip-like factors.

i) Treatment of overdoses of FK-506, rapamycin, immunosuppressive Novel Compounds, and other macrophilin binding immunosuppressants.

The invention thus provides the Novel Compounds described herein, for use as novel intermediates or as pharmaceuticals, methods of treating or preventing the above-described disorders by administering an effective amount of a Novel Compound to a patient in need thereof, use of a Novel Compound in the manufacture of a medicament for treatment or prevention of the above-described disorders, and pharmaceutical compositions comprising a Novel Compound in combination or association with a pharmaceutically acceptable diluent or carrier.

Most of the Novel Compounds described herein are highly immunosuppressive, especially those Novel Compounds which are O-substituted at C40, and these Novel Compounds are particularly useful in indications a and b, but not in indication i. Those of the Novel Compounds which are less immunosuppressive, especially those which are O-substituted at C28 only, are particularly useful in indications h and i, but are less preferred in indications a or b.

The Novel Compound s are utilized by administration of a pharmaceutically effective dose in pharmaceutically

acceptable form to a subject in need of treatment. Appropriate dosages of the Novel Compounds will of course vary, e.g. depending on the condition to be treated (for example the disease type or the nature of resistance), the effect desired and the mode of administration.

In general however satisfactory results are obtained on administration orally at dosages on the order of from 0.05 to 5 or up to 10 mg/kg/day, e.g. on the order of from 0.1 to 2 or up to 7.5 mg/kg/day administered once or, in divided doses 2 to 4× per day, or on administration parenterally, e.g. intravenously, for example by i.v. drip or infusion, at dosages on the order of from 0.01 to 2.5 up to 5 mg/kg/day, e.g. on the order of from 0.05 or 0.1 up to 1.0 mg/kg/day. Suitable daily dosages for patients are thus on the order of 500 mg p.o., e.g. on the order of from 5 to 100 mg p.o., or on the order of from 0.5 to 125 up to 250 mg i.v., e.g. on the order of from 2.5 to 50 mg i.v.

Alternatively and even preferably, dosaging is arranged in patient specific manner to provide pre-determined trough blood levels, e.g. as determined by RIA technique. Thus patient dosaging may be adjusted so as to achieve regular on-going trough blood levels as measured by RIA on the order of from 50 or 150 up to 500 or 1000 ng/ml, i.e. analogously to methods of dosaging currently employed for Ciclosporin immunosuppressive therapy.

The Novel Compounds may be administered as the sole active ingredient or together with other drugs. For example, in immunosuppressive applications such as prevention and treatment of graft vs. host disease, transplant rejection, or autoimnune disease, the Novel Compounds may be used in combination with Ciclosporin, FK-506, or their immunosuppressive derivatives; corticosteroids; azathioprene; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to CD3, CD4, CD25, CD28, or CD45; and 7or other immunomodulatory compounds. For anti-inflammatory applications, the Novel Compounds can be used together with anti-inflammatory agents, e.g., corticosteroids. For anti-infective applications, the Novel Compounds can be used in combination with other anti-infective agents, e.g., anti-viral drugs or antibiotics.

The Novel Compounds are administered by any conventional route, in particular enterally. e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Suitable unit dosage forms for oral administration comprise, e.g. from 1 to 50 mg of a compound of the invention, usually 1 to 10 mg. Pharmaceutical compositions comprising the novel compounds may be prepared analogously to pharmaceutical compositions comprising rapamycin, e.g., as described in EPA 0 041 795, which would be evident to one skilled in the art.

The pharmacological activity of the Novel Compounds are demonstrated in, e.g.. the following tests:

1. Mixed Lymphocyte Reaction (MLR)

The Mixed Lymphocyte Reaction was originally developed in connection with allografts, to assess the tissue compatibility between potential organ donors and recipients, and is one of the best established models of immune reaction in vitro. A murine model MLR, e.g., as described by T. Meo in "Immunological Methods", L. Lefkovits and B. Peris, Eds., Academic Press, N.Y. pp. 227–239 (1979), is used to demonstrate the immunosuppressive effect of the Novel Compounds. Spleen cells (0.5×10^6) from Balb/c mice (female, 8–10 weeks) are co-incubated for 5 days with 0.5×10^6 irradiated (2000 rads) or mitomycin C treated spleen cells from CBA mice (female, 8–10 weeks). The irradiated allogeneic cells induce a proliferative response in the Balb/c spleen cells which can be measured by labeled precursor incorporation into the DNA. Since the stimulator cells are irradiated (or mitomycin C treated) they do not respond to the Balb/c cells with proliferation but do retain their antigenicity. The antiproliferative effect of the Novel Compounds on the Balb/c cells is measured at various dilutions and the concentration resulting in 50% inhibition of cell proliferation (IC_{50}) is calculated. The inhibitory capacity of the test sample may be compared to rapamycin and expressed as a relative IC_{50} (i.e. IC_{50} test sample/IC_{50} rapamycin).

2. IL-6 Mediated Proliferation

The capacity of the Novel Compounds to interfere with growth factor associated signalling pathways is assessed using an interleukin-6 (IL-6)-dependent mouse hybridoma cell line. The assay is performed in 96-well microtiter plates. 5000 cells/well are cultivated in serum-free medium (as described by M. H. Schreier and R. Tees in Immunological Methods, I. Lefkovits and B. Pernis, eds., Academic Press 1981, Vol. II, pp. 263–275), supplemented with 1 ng recombinant IL-6/ml. Following a 66 hour incubation in the absence or presence of a test sample, cells are pulsed with 1 μCi (3-H)-thymidine/well for another 6 hours, harvested and counted by liquid scintillation. (3-H)-thymidine incorporation into DNA correlates with the increase in cell number and is thus a measure of cell proliferation. A dilution series of the test sample allows the calculation of the concentration resulting in 50% inhibition of cell proliferation (IC_{50}). The inhibitory capacity of the test sample may be compared to rapamycin and expressed as a relative IC_{50} (i.e. IC_{50} test sample/IC_{50} rapamycin).

3. Macrophilin Binding Assay

Rapamycin and the structurally related immunosuppressant, FK-506, are both known to bind in vivo to macrophilin-12 (also known as FK-506 binding protein or FKBP-12), and this binding is thought to be related to the immunosuppressive activity of these compounds. The Novel Compounds also bind strongly to macrophilin-12, as is demonstrated in a competitive binding assay.

In this assay, FK-506 coupled to BSA is used to coat micronier wells. Bioonyiated recombinant human macrophilin-12 (biot-MAP) is allowed to bind in the presence or absence of a test sample to the immobilized FK-506. After washing (to remove non-specifically bound macrophilin), bound biot-MAP is assessed by incubation with a streptavidin-alkaline phosphatase conjugate, followed by washing and subsequent addition of p-nitrophenyl phosphate as a substrate. The read-out is the OD at 405 nm. Binding of a test sample to biot-MAP results in a decrease in the amount of biot-MAP bound to the FK-506 and thus in a decrease in the OD405. A dilution series of the test sample allows determination of the concentration resulting in 50% inhibition of the biot-MAP binding to the immobilized FK-506 (IC_{50}). The inhibitory capacity of a test sample is compared to the IC_{50} of free FK-506 as a standard and expressed as a relative IC_{50} (i.e., IC_{50}-test sample/ IC_{50}-free FK-506).

4. Localized Graft-Versus-Host (GvH) Reaction

In vivo efficacy of the Novel Compounds is proved in a suitable animal model, as described, e.g., in Ford et al, TRANSPLANTATION 10 (1970) 258. Spleen cells (1×10^7) from 6 week old female Wistar/Furth (WF) rats are injected subcutaneously on day 0 into the left hind-paw of female (F344×WF)F_1 rats weighing about 100 g. Animals are treated for 4 consecutive days and the popliteal lymph nodes are removed and weighed on day 7. The difference in weight between the two lymph nodes is taken as the parameter for evaluating the reaction.

5. Kidney Allograft Reaction in Rat

One kidney from a female fisher 344 rat is transplanted onto the renal vessel of a unilaterally (left side) nephrectomized WF recipient rat using an end-to-end anastomosis. Ureteric anastomosis is also end-to-end. Treatment commences on the day of transplantation and is continued for 14 days. A contralateral nephrectomy is done seven days after transplantation, leaving the recipient relying on the performance of the donor kidney. Survival of the graft recipient is taken as the parameter for a functional graft.

6. Experimentally Induced Allergic Encephalomyelitis (EAE) in Rats

Efficacy of the Novel Compounds in EAE is measured, e.g., by the procedure described in Levine & Wenk, AMER J PATH 47 (1965) 61; McFarlin et al, J IMMUNOL 113 (1974) 712; Borel, TRANSPLANT. & CLIN. IMMUNOL 13 (1981) 3. EAE is a widely accepted model for multiple sclerosis. Male Wistar rats are injected in the hind paws with a mixture of bovine spinal cord and complete Freund's adjuvant. Symptoms of the disease (paralysis of the tail and both hind legs) usually develop within 16 days. The number of diseased animals as well as the time of onset of the disease are recorded.

7. Freund's Adjuvant Arthritis

Efficacy against experimentally induced arthritis is shown using the procedure described. e.g., in Winter & Nuss, ARTHRITIS & RHEUMATISM 9 (1966) 394; Billingham & Davies, HANDBOOK OF EXPERIMENTAL PHARMACOL (Vane & Ferreira Eds. Springer-Verlag, Berlin)50/II (1979) 108–144. OFA and Wistar rats (male or female, 150 g body weight) are injected i.c. at the base of the tail or in the hind paw with 0.1 ml of mineral oil containing 0.6 mg of lyophilized heat-killed Mycobacterium smegmatis. In the developing arthritis model, treatment is started immediately after the injection of the adjuvant (days 1–18); in the established arthritis model treatment is started on day 14, when the secondary inflammation is well developed (days 14–20). At the end of the experiment, the swelling of the joints is measured by means of a micro-caliper. ED_{50} is the oral dose in mg/kg which reduces the swelling (primary or secondary) to half of that of the controls.

8. Antitumor and MDR Activity

The antitumor activity of the Novel Compounds and their ability to enhance the performance of antitumor agents by alleviating multidrug resistance is demonstrated, e.g., by administration of an anticancer agent, e.g., colchicine or etoposide, to multidrug resistant cells and drug sensitive cells in vitro or to animals having multidrug resistant or drug sensitive tumors or infections, with and without co-administration of the Novel Compounds to be tested, and by administration of the Novel Compound alone.

Such in vitro testing is performed employing any appropriate drug resistant cell line and control (parental) cell line, generated e.g. as described by Ling et al., J. Cell. Physiol. 83, 103–116 (1974) and Bech-Hansen et al. J. Cell. Physiol. 88,23–32 (1976). Particular clones chosen are the multi-drug resistant (e.g. colchicine resistant) line CHR (subclone C5S3.2) and the parental sensitive line AUX B1 (subclone AB1 S11).

In vivo anti-tumor and anti-MDR activity is shown, e.g., in mice injected with multidrug resistant and drug sensitive cancer cells. Ehrlich ascites carcinoma (EA) sub-lines resistant to drug substance DR, VC, AM, ET, TE or CC are developed by sequential transfer of EA cells to subsequent generations of BALB/c host mice in accordance with the methods described by Slater et al., J. Clin. Invest, 70, 1131 (1982).

Equivalent results may be obtained employing the Novel Compounds test models of comparable design, e.g. in vitro, or employing test animals infected with drug-resistant and drug sensitive viral strains, antibiotic (e.g. penicillin) resistant and sensitive bacterial strains, anti-mycotic resistant and sensitive fungal strains as well as drug resistant protozoal strains, e.g. Plasmodial strains, for example naturally occurring sub-strains of Plasmodium falciparum exhibiting acquired chemotherapeutic, anti-malarial drug resistance.

9. FKBP Binding

Certain of the Novel Compounds are not immunosuppressive, particularly those which are O-substituted at C28 only, such as 28-O-methyl-rapamycin. This can be shown in standard in vitro assays in comparison to FK506 and rapamycin. FK506, for example, is known to be a potent inhibitor of IL-2 transcription, as can be shown in an IL-2 reporter gene assay. Rapamycin, although not active in the IL-2 reporter gene assay, strongly inhibits IL-6 dependent T-cell proliferation. Both compounds are very potent inhibitors of the mixed lymphocyte reaction. Nonimmunosuppressivity can also be shown in the in vivo models 1–7 above. Even those Novel Compounds which are not immunosuppressive, however, bind to macrophilin, which confers certain utilities in which nonimmunosuppressivity is an advantage.

Those of the Novel Compounds which bind strongly to macrophilin and are not themselves immunosuppressive can be used in the treatment of overdoses of macrophilin-binding immunosuppressants, such as FK506, rapamycin, and the immunosuppressive Novel Compounds.

10. Steroid Potentiation

The macrophilin binding activity of the Novel Compounds also makes them useful in enhancing or potentiating the action of corticosteroids. Combined treatment with the compounds of the invention and a corticosteroid, such as dexamethasone, results in greatly enhanced steroidal activity. This can be shown. e.g., in the murine mammary tumor virus-chloramphenicol acetyltransferase (MMTV-CAT) reporter gene assay, e.g., as described in Ning, et al., *J. Biol. Chem.* (1993) 268: 6073. This synergistic effect allows reduced doses of corticosteroids, thereby reducing the risk of side effects in some cases.

11. Mip and Mip-like Factor Inhibition

Additionally, the Novel Compounds bind to and block a variety of Mip (macrophage infectivity potentiator) and Mip-like factors, which are structurally similar to macro-

philin. Mip and Mip-like factors are virulence factors produced by a wide variety of pathogens, including those of the genera Chlamidia, e.g., *Chlamidia trachomatis;* Neisseria, e.g., *Neisseria meninngitidis* and Legionella, e.g., *Legionella pneumophilia;* and also by the obligately parasitic members of the order Rickettsiales. These factors play a critical role in the establishment of intracellular infection. The efficacy of the Novel Compounds in reducing the infectivity of pathogens which produce Mip or Mip-like factors can be shown by comparing infectivity of the pathogens in cells culture in the presence and absence of the macrolides, e.g., using the methods described in Lundemose, et al., *Mol. Microbiol.* (1993) 7: 777. The nonimmunosuppressive compounds of the invention are preferred for use in this indication for the reason that they are not immunosuppressive, thus they do not compromise the body's natural immune defenses against the pathogens.

The Novel Compounds are also useful in assays to detect the presence or amount of macrophilin-binding compounds, e.g., in competitive assays for diagnostic or screening purposes. Thus, in another embodiment, the invention provides for use of the Novel Compounds as a screening tool to determine the presence of macrophilin-binding compounds in a test solution, e.g., blood, blood serum, or test broth to be screened. Preferably, a Novel Compound is immobilized in microtiter wells and then allowed to bind in the presence and absence of a test solution to labelled macrophilin-12 (FKBP-12). Alternatively, the FKBP-12 immobilized in microtiter wells and allowed to bind in the presence and absence of a test solution to a Novel Compound which has been labelled, e.g., fluoro-, enzymatically- or radio-labelled, e.g., a Novel Compound which has been O-substituted at C40 and/or C28 with a labelling group. The plates are washed and the amount of bound labelled compound is measured. The amount of macrophilin-binding substance in the test solution is roughly inversely proportional to the amount of bound labelled compound. For quantitative analysis, a standard binding curve is made using known concentrations of macrophilin bind compound.

EXAMPLES

In the following examples, characteristic spectroscopic data is given to facilitate identification. Peaks which do not differ significantly from rapamycin are not included. Biological data is expressed as a relative IC_{50}, compared to rapamycin in the case of the mixed lymphocyte reaction (MLR) and IL-6 dependent proliferation (IL-6 dep. prol.) assays, and to FK-506 in the macrophilin binding assay (MBA). A higher IC_{50} correlates with lower binding affinity.

Example 1

40-O-Benzyl-rapamvein

To a stirred solution of 183 mg (0.200 mmol) of rapamycin in 2.1 mL of 2:1 cyclohexane-methylene chloride is added 75 μL (0.402 mmol) of benzyl-trichloroacetimidate, followed by 2.6 μL (29 mmol 15 mol %) of trifluoromethanesulfonic acid whereupon the mixture turned immediately yellow. After 3 h the mixture is diluted with ethyl acetate and quenched with 10% aqueous sodium bicarbonate. The layers are separated and the aqueous layer is extracted twice with ethyl acetate. The combined organic solution is washed with 10% aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel (50:50 hexane-ethyl acetate) to afford 40-O-benzyl-rapamycin as a white amorphous solid: ^1H NMR ($CDCl_3$) δ0.73 (1H, dd), 1.65 (3H, s), 1.73 (3H, s), 3.12 (4H, s and m). 3.33 (3H, s), 3.49 (3H, s), 4.15 (1H, bd), 4.65 (1H, d), 4.71 (1H, d), 7.22–7.38 (5H, m): MS (FAB) m/z 1026 ($[M+Na]^+$), 972 ($[M—OCH_3)]^+$), 954 ($[M—(OCH_3+H_2O)]^+$).

MBA (rel. IC50)	1.8
IL-6 dep. prol. (rel. IC50)	10
MLR (rel. IC50)	110

Example 2

40-O-(4'-Hydroxymethyl)benzyl-rapamvein

a) 40-O-[4'-(t-Buryldimethylsilyl)oxymethyl]benzyl-rapamycin

To a stirred, cooled (−78° C.) solution of 345 μL (2.0 mmol) of triflic anhydride in 5 mL of methylene chloride is added a solution of 504 mg (2.0 mmol) of 4 -(t-butyldimethylsilyl)oxymethyl-benzyl alcohol and 820 mg (4.0 mmol) of 2,6-di-t-buryl-4-methyl-pyridine in 5 mL of methylene chloride. The resulting mixture is warmed to −20° C. and stirring is continued at this temperature for 0.5 h. The mixture is then cooled back to −78° C. and a solution of 914 mg (1.0 mmol) of rapamycin in 5 mL of methylene chloride is added. This mixture is allowed to warm to room temperature overnight and is then quenched with 10% aqueous sodium bicarbonate. The layers are separated and the aqueous layer is extracted with ethyl acetate. The combined organic solution is washed with saturated brine, dried over sodium sulfate, filtered under reduced pressure and concentrated. The residue is purified by column chromatography on silica gel (50:50 hexane-ethyl acetate) to afford 40-O-[4'-(t-butyldimethylsilyl)oxymethyl]benzyl-rapamycin a white foam: MS (FAB) m/z 1170 ($[M+Na]^+$), 1098 ($[M—(OCH_3+H_2O)]^+$).

b) 40-O-(4'-Hydroxymethyl)benzyl-rapamycin

To a stirred, cooled (0° C.) solution of 98 mg (0.093 mmol) of the compound obtained in example 2 in 2 mL of acetonitrile is added 0.2 mL of HF-pyridine. The resulting mixture is stirred for 2 h and quenched with aqueous sodium bicarbonate, then extracted with ethyl acetate. The organic solution is washed with brine, dried over sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (20:80 hexane-ethyl acetate) to afford the title compound as a white foam: ^1H NMR ($CDCl_3$) δ0.73 (1H, dd), 1.65 (3H, s), 1.74 (3H, s), 3.22 (1H, m), 4.67 (4H, m), 7.35 (4H, m); MS (FAB) m/z 1056 ($[M+Na]^+$), 1002 ($[M—OCH_3]^+$), 984 ($[M—(OCH_3+H_2)]^+$), 966 ($[M—(OCH_3+2H_2O)]^+O$). 934 ($[M—(OCH_3+CH_3OH+2H_2O)]^+$).

MBA (rel. IC50)	2.7
IL-6 dep. prol. (rel. IC50)	3.9
MLR (rel. IC50)	3

Example 3

40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin

a) 40-O-[4'-(2,2-Dimethyl-1,3-dioxolan-4-yl)]benzyl-rapamycin

In 10 mL of 1:1 cyclohexane-methylene chloride is dissolved 452 mg (1.24 mmol) of 4-(2,2-dimethyl-1,3-dioxolan-4yl)benzyl trichloroaceamidate, followed by 0.14 mL (0.64 mmol) of 2,6di-t-butylpyridine and 56 μL (0.64 mmol) of trifluoromethanesulfonic acid. To this mixture is added a solution of 587 mg (0.64 mmol) of rapamycin in 2 mL of methylene chloride. The reaction is stirred overnight at room temperature and quenched with aqueous sodium bicarbonate. The layers are separated and the aqueous layer is extracted twice with ethyl acetate. The combined organic solution is washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (50:50 hexane-ethyl acetate) to give 40-O-[4'-(2,2-Dimethyl-1,3-dioxolan-4-yl)]benzyl-rapamycin as a white, amorphous solid: ^{1}H NMR ($CDCl_3$) δ0.73 (1H, dd), 1.48 (3H, s), 1.55 (3H, s), 1.65 (3H, s), 1.74 (3H, s), 3.67 (3H, m), 4.28 (1H, dd), 4.62 (1H, d), 4.69 (1H, d), 5.06 (1H, dd), 7.33 (4H, m); MS (FAB) m/z 1126 ([M+Na]$^+$), 1072 ([M—OCH_3]$^+$), 1054 ([M—(OCH_3+H_2O)]$^+$), 1014 ([M—(OCH_3+CH_3COCH_3)]$^+$), 966 ([M—(OCH_3+H_2O+CH_3COCH_3)]$^+$, 978 (M—(OCH_3+2_2O+CH_3COCH_3)]$^+$).

b) 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin

To a solution of 90.7 mg (0.08 mmol) of 40-O-[4'-(2,2-Dimethyl-1,3-dioxolan-4-yl)]benzyl-rapamycin in 4 mL of methanol is added 1 mL of 1N aqueous HCl. After 2 h the mixture is quenched with aqueous sodium bicarbonate and extracted twice with ethyl acetate. The organic solution is washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue is purified by column chromatography on silica gel (ethyl acetate) and the title compound is obtained as a white foam: ^{1}H NMR ($CDCl_3$) δ0.73 (1H, dd), 1.65 (3H, 5), 1.74 (3H, s), 3.70 (4H, m), 4.63 (1H, d), 4.69 (1H, d), 4.80 (1H, dd), 7.33 (4H, m); MS (FAB) m/z 1086 ([M+Na]$^+$), 1032 ([M—OCH_3]$^+$), 1014 ([M—(OCH_3+H_2O)]$^+$), 996 ([M—(OCH_3+$2H_2O$)]$^+$).

MBA (rel. IC50)	0.92
IL-6 dep. prol. (rel. IC50)	10.5
MLR (rel. IC50)	22

Example 4

40-O-Allyl-rapamvcin

To a stirred, cooled (−78° C.) solution of 0.33 mL (2.01 mmol) of triflic anhydride in 10 mL of methylene chloride is slowly added a solution of 0.14 mL (2.06 mmol) of allyl alcohol and 0.42 g (2.04 mmol) of 2,6-di-t-butyl-4-methyl-pyridine in 5 mL of methylene chloride. The resulting greenish solution is stirred for 1.5 h and a solution of 915 mg (1.00 mmol) of rapamycin and 0.42 g (2.04 mmol) of 2,6-di-t-butyl-4-methyl-pyridine in 5 mL of methylene chloride is added. Stirring is continued for 0.5 h at −78° C. and then the mixture is warmed to room temperature. After one more hour the mixture is quenched with aqueous sodium bicarbonate and the layers are separated. The aqueous layer is extracted twice with ethyl acetate. The combined organic solution is washed with aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting green oil is purified by column chromatography on silica gel (60:40 hexane-ethyl acetate) to afford the title compound as a colorless, amorphous solid: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.74 (3H, s), 3.05 (1H, m), 4.13 (2H, bd), 5.14 (2H, m), 5.27 (2H, m), 5.92 (2H, m); MS (FAB) m/z 976 ([M+Na]$^+$), 922 ([M—OCH_3]$^+$), 904 ([M—(OCH_3+H_2O)]$^+$). 866 ([M—OCH_3+$2H_2O$)]$^+$), 872 ([M—($2CH_3OH$+OH)]$^+$), 854 ([M—(OCH_3+CH_3OH+$2H_2O$)]$^+$).

MBA (rel. IC50)	1
IL-6 dep. prol. (rel. IC50)	8
MLR (rel. IC50)	260

Example 5

40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin

To a stirred, cooled (−78° C.) solution of 0.64 g (4.00 mmol) of E-(4S)4,5-O,O-isopropylidene-pent-2-en-1,4,5-triol and 1.26 g (6.00 mmol) of 2,6-di-t-butyl-4-methyl-pyridine in 20 mL of methylene chloride is added 0.82 mL (5.00 mmol) of triflic anhydride. The resulting mixture is stirred at this temperature for 2 h and a solution of 1.82 g (2.00 mmol) of rapamycin and 1.26 g (6.00 mmol) of 2,6di-t-butyl-4-methyl-pyridine in 5 mL of methylene chloride is added. The mixture is allowed to gradually warm to room temperature overnight and is then quenched with aqueous sodium bicarbonate. The layers are separated and the aqueous layer is extracted three times with ethyl acctate. The organic solution is washed with aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate. filtered and concentrated. The residue is purified by column chromatography on silica gel (40:60 hexane-ethyl acetate) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.38 (3H, s), 1.42 (3H, s), 1.65 (3H, s), 1.73 (3H, s), 3.06 (1H, m), 3.58 (2H, m), 4.08 (1H, dd), 4.15 (2H, m), 4.52 (1H, bdd), 5.72 (1H, m), 5.88 (1H, m); MS (FAB) m/z 1076 ([M+Na]$^+$), 1022 ([M—OCH_3]$^+$), 1004 ([M—(OCH_3+H_2O)]$^+$), 964 ([M—(OCH_3+CH_3COCH_3)]$^+$), 946 ([M—(OCH_3+H_2O+CH_3COCH_3)]$^+$), 946 ([M—(OCH_3+$2H_2O$+CH_3COCH_3)]$^+$).

MBA (rel. IC50)	0.64
IL-6 dep. prol. (rel. IC50)	11
MLR (rel. IC50)	8

Example 6

(2'E, 4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl-rapamycin

The conditions described in example 3, step b) applied to the compound obtained in in the previous example, followed by purification through column chromatography on silica gel (95:5 ethyl acetate-methanol) afford the title compound as a white foam: ^{1}H NMR ($CDCl_3$) δ0.68 (1H, dd), 3.04 (1H, m), 4.18 (5H, m), 5.75 (1H, dd), 5.88 (1H, m); MS (FAB) m/z 1036 ([M+Na]$^+$), 1013 (M$^+$), 995 ([M—H_2O]$^+$), 982 ([M—OCH_3]$^+$), 964 ([M—(OCH_3+H_2O)]$^+$), 946 (M—(OCH_3+$2H_2O$)]$^+$), 832 (M—([$2CH_3OH$+OH)]$^+$), 914 ([M—(OCH_3+CH_3OH+$2H_2O$)]$^+$).

MBA (rel. IC50)	1.7
IL-6 dep. prol. (rel. IC50)	12
MLR (rel. IC50)	3.5

Example 7

40-O-(2-Hydroxy)ethoxycarbonvimethyl-ranamycin

a) 40-O-[2-(t-Butyldimethylsilyl)oxy) ethoxycarbonylmethyl-rapamycin

To a stirred solution of 2.74 g (3.00 mmol) of rapamycin and 30 mg (0.06 mmol) of dirhodium tetracetate dihydrate in 30 mL of methylene chloride is added a solution of 0.38 mL (3.60 mmol) of 2-(t-buryldimethylsilyl)oxyethyl diazoacetate in 10 mL of methylene chloride over 5 h. After the addition is complete stirring is continued for one more hour, then the reaction is quenched with 1N aq. HCl. The layers are separated and the aqueous layer is extracted with ethyl acetate. The combined organic solution is washed with aq. sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (40:60 hexane-ethyl acetate) yielding 40-O-[2-(t-butyldimethylsilyl)oxy] ethoxycarbonylmethyl-rapamycin: ^{1}H NMR ($CDCl_3$) δ0.06 (6H, s), 0.68 (1H, dd), 0.88 (9H, s), 1.64 (3H, s), 1.73 (3h, s), 3.12 (5H, s and m), 3.81 (2H, dd), 4.19 (2H, dd), 4.32 (2H, s); MS (FAB) m/z 1152 ([M+Na]$^+$), 1080 ([M—(OCH_3+H_2O)]$^+$).

b) 40-O-(2-Hydroxy)ethoxycarbonylmethyl-rapamycin

To a stirred, cooled (0° C.) solution of 81 mg (0.07 mmol) of 40-O-[2-(t-buryldimethylsilyl)oxy] ethoxycarbonylmethyl-rapamycin in 1.5 mL of acetonitrile is added 0.15 mL of HF-pyridine. After 2 h the reaction is quenched with aq. sodium bicarbonate. The mixture is extracted with ethyl acetate. The organic solution is washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by PTLC (ethyl acetate) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.70 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 3.13 (5H, s and m), 3.85 (3H, m), 4.25 (5H, m); MS (FAB) m/z 1038 ([M+Na]$^+$), 984 ([M—OCH_3]$^+$), 966 ([M—(OCH_3+H_2O)]$^+$), 948 ([M—(OCH_3+$2h_2O$)]$^+$).

MBA (rel. IC50)	4
IL-6 dep. prol. (rel. IC50)	9.7
MLR (rel. IC50)	2.1

Example 8

40-O-(2-Hydroxy)ethyl-rapamycin

a) 40-O-[2-(t-Buryldimethylsilyl)oxy]ethyl-rapamycin

A solution of 9.14 g (10 mmol) of rapamycin and 4.70 mL (40 mmol) of 2,6-lutidine in 30 mL of toluene is warmed to 60° C. and a solution of 6.17 g (20 mmol) of 2-(t-butyldimethylsilyl)oxyethyl triflate and 2.35 mL (20 mmol) of 2,6-lutidine in 20 mL of toluene is added. This mixture is stirred for 1.5 h. Then two batches of a solution of 3.08 g (10 mmol) of trifate and 1.2 mL (10 mmol) of 2,6-lutidine in 10 mL of toluene are added in a 1.5 h interyal. After addition of the last batch, stirring is continued at 60° C. for 2 h and the resulting brown suspension is filtered. The filtrate is diluted with ethyl acetate and washed with aq. sodium bicarbonate and brine. The organic solution is dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (40:60 hexane-ethyl acetate) to afford 40-O-2-(t-buryldimethylsilyl)oxy]ethyl-rapamycin as a white solid: ^{1}H NMR ($CDCl_3$) δ0.06 (6H, s), 0.72 (1H, dd), 0.90 (9H, s), 1.65 (3H, s), 1.75 (3H, s), 3.02 (114, m), 3.63 (3H, m), 3.72 (3H, m); MS (FAB). m/z 1094 ([M+Na]$^+$), 1022 ([M—(OCH_3+H_2O)]$^+$).

b) 40-O-(2-Hydroxy)ethyl-rapamycin

To a stirred, cooled (0° C.) solution of 4.5 g (4.2 mmol) of 40-O-[2-(t-buryldimethylsilyl)oxy]ethyl-rapamycin in 20 mL of methanol is added 2 mL of 1N HCl. This solution is stirred for 2 h and neutralized with aq. sodium bicarbonate. The mixture is extracted with three portions of ethyl acetate. The organic solution is washed with aq. sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated. Purification by column chromatography on silica gel (ethyl acetate) gave the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 3.13 (5H, s and m), 3.52–3.91 (8H, m); MS (FAB) m/z 980 ([M+Na]$^+$), 926 ([M—OCH_3]$^+$), 908 ([M—OCH_3+H_2O)]$^+$), 890 ([M—(OCH_3+$2H_2O$)]$^+$), 876 ([M—($2CH_3OH$+OH)]$^+$), 858 ([M—(OCH_3+CH_3OH+$2H_2O$)]$^+$).

MBA (rel. IC50)	2.2
IL-6 dep. prol. (rel. IC50)	2.8
MLR (rel. IC50)	3.4

Example 9

40-O-(3-Hydroxy)propyl-rapamycin

a) 40-O-(3-(t-Butyldimethysilyl)oxy]propyl-rapamycin

The same procedure as described in example 8, step a) using 3-(t-butyldimethylsilyl)oxyprop-1-yl triflate affords 40-O-3-(t-butyldimethylsilyl)oxy]propyl-rapamycin: ^{1}H NMR ($CDCl_3$) δ0.05 (6H, s), 0.72 (1H, dd), 0.90 (9H, s), 1.65 (3H, s), 1.74 (3H, s), 1.77 (2H, m), 3.03 (1H, m), 3.52–3.73 (7H, m); MS (FAB) m/z 1108 ([(M+Na]$^+$), 1036 (M—(OCH_3+H_2O)]$^+$).

b) 40-O-(3-Hydroxy)propyl-rapamycin

Treatment of the compound obtained in step a) in the conditions described in example 8, step b) yields the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 1.80 (2H, m), 3.05 (1H, m), 3.55–3.91 (8H, m); MS (FAB) m/z 994 ([M+Na]$^+$), 940 ([M—OCH_3]$^+$), 922 ([M—(OCH_3+H_2O)]$^+$), 904 ([M—(OCH_3+(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	1.6
IL-6 dep. prol. (rel. IC50)	2.7
MLR (rel. IC50)	11

Example 10

40-O-(6-Hydroxy)hexyl-rapamycin

a) 40-O-[6-(t-Butyldimethylsilyl)oxy]hexyl-rapamycin

The same procedure as described in example 8, step a) using 6-(t-butyldimethylsilyl)oxyhexyl tiflate affords 40-O-[6-(t-Buryldimethylsilyl)oxy]hexyl-rapamycin: MS (FAB) m/z 1150 ([M+Na]$^+$).

b) 40-O-(6-Hydroxy)hexyl-rapamycin

Treatment of the compound obtained in step a) in the conditions described in example 8. step b) yields the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.38 (2H, m), 1.57 (4H, m), 1.65 (3H, s), 1.74 (3H, s), 3.02 (1H, m), 3.49–3.72 (8H, m); MS (FAB) m/z 1036 ([M+Na]$^+$), 982 ([M—OCH_3]$^+$), 964 ([M—(OCH_3+H_2))]$^+$), 946 ([M—(OCH_3+2H_2O)]$^+$).

MBA (rel. IC50)	0.8
IL-6 dep. prol. (rel. IC50)	8.5
MLR (rel. IC50)	18

Example 11

40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin

a) 40-O-[2-(t-Buryldimethylsilyl)oxyethoxy]ethyl-rapamycin

The same procedure as described in example 8, step a) using 2-[2-(t-butyldimethylsilyl)oxy-ethoxy]ethyl tnflate affords 40-O-[2-(t-butyldimethylsilyl)oxyethoxy]ethyl-rapamycin: ^{1}H NMR ($CDCl_3$) δ0.06 (6H, s), 0.71 (1H, dd), 0.88 (9H, s), 1.65 (3H, s), 1.74 (3.07 (1H, m), 3.51–3.79 (11H, m); MS (FAB) m/z 1138 ([M+Na]$^+$), 1115 (M$^+$), 1097 ([M—H_2O]$^+$), 1084 ([M—OCH_3]$^+$), 1066 ([M—(OCH_3+H_2O)]$^+$), 1048 ([M—(OCH_3+2H_2O)]$^+$), 1034 ([M—(2CH_3OH+OH)]$^+$), 1016 ([M—(OCH_3+CH_3OH+2H_2O)]$^+$).

b) 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin

Treatment of the compound obtained in step a) in the conditions described in example 8, step b) yields the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.74 (3H, s), 3.05 (1H, m), 3.51–3.77 (11H, m); MS (FAB) m/z 1024 ([M+Na]$^+$), 1001 (M$^+$), 983 ([M—H_2O]$^+$), 970 ([M—OCH_3]$^+$), 952 ([M—(OCH_3+H_2O)]$^+$), 934 ([M—(OCH_3+2H_2O)]$^+$), 920 ([M—(2CH_3OH+OH)]$^+$), 902 ([M—(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	1.2
IL-6 dep. prol. (rel. IC50)	3.2
MLR (rel. IC50)	2

Example 12

40-O-[(3S)-2,2-Dimethyldioxolan-3-yl]methyl-rapamycin

The same procedure as described in example 8, step a) using the tiflate of glycerol acetonide affords the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.36 (3H, s), 1.42 (3H, s), 1.65 (3H, s), 1.75 (3H, s), 3.06 (1H, m), 3.55 (2H, m), 3.69 (3H, m), 4.06 (1H, dd), 4.26 (1H, m); MS (FAB) m/z 1050 ([M+Na]$^+$), 996 ([M—OCH_3]$^+$), 978 ([M—(OCH_3+H_2O)]$^+$), 960 ([M—(OCH_3+2H_2O)]$^+$).

MBA (rel. IC50)	0.9
IL-6 dep. prol. (rel. IC50)	8
MLR (rel. IC50)	290

Example 13

40-O-[(2S)-2,3-Dihydroxyprop-1-yl]-rapamycin

Treatment of the compound obtained in the previous example in the conditions described in example 3 yields the title compound: ^{1}H NMR ($CDCl_3$) 67 0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 3.07 (1H, m), 3.68 (8H, m); MS (FAB) m/z 1010 ([M+Na]$^+$), 956 ([M—OCH_3]$^+$), 938 ([M—(OCH_3+H_2O)]$^+$), 920 ([M—(OCH_3+2H_2O)]$^+$), 888 ([M—(OCH_3+CH_3OH 2H_2O)]$^+$).

MBA (rel. IC50)	0.67
IL-6 dep. prol. (rel. IC50)	9
MLR (rel. IC50)	10

Example 14

40-O-(2-Acetoxy)ethyl-rapamycin

To a stirred, cooled (0° C.) solution of 53 mg (0.055 mmol) of 40-O-hydroxyethyl-rapamycin in 2 mL of methylene chloride is added 0.2 mL of pyridine followed by 0.02 mL (0.281 mmol) of acetyl chloride. The mixture is stirred

for 3 h and diluted with ethyl acetate, then washed with aq. sodium bicarbonate, cold 1N HCl and again with aq. sodium bicarbonate. The organic solution is dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (30:70 hexane-ethyl acetate) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 2.08 (3H, s), 3.07 (1H, m), 3.78 (2H, dd), 4.20 (2H, dd); MS (FAB) m/z 1022 ([M+Na]$^+$), 999 (M$^+$), 982 ([M—OH]$^+$), 968 ([M—OCH_3]$^+$), 950 ([M—(OCH_3+H_2O)]$^+$), 932 ([M—(OCH_3+2H_2O)]$^+$), 918 ([M-(2CH_3OH+OH)]$^+$), 900 ([M—(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	2
IL-6 dep. prol. (rel. IC50)	7.6
MLR (rel. IC50)	3.6

Example 15

40-O-(2-Nicotinoyloxy)ethyl-rapamycin

The same procedure as described in the previous example using nicotinoyl chloride hydrochloride affords the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 3.07 (1H, m), 3.94 (2H, dd), 4.49 (2H, t), 7.39 (1H, dd), 8.31 (1H, ddd), 8.78 (1H, ddd), 9.24 (1H, dd); MS (FAB) m/z 1085 ([M+Na]$^+$), 1063 ([M+H]$^+$), 1045 ([M—OH]$^+$), 1031 ([M—OCH_3]$^+$), 1013 ([M—(OCH_3+H_2O)]$^+$).

MBA (rel. IC50)	1.1
IL-6 dep. prol. (rel. IC50)	6.9
MLR (rel. IC50)	5

Example 16

40-O-(2-(N-Morpholino)acetoxy]ethyl-rapamycin

a) 40-O-(2-Bromoacetoxy)ethyl-rapamycin

The same procedure as described in example 14 using bromoacetyl chloride affords 40-O-(2-bromoacetoxy)ethyl-rapamycin: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.67 (3H, s), 1.76 (3H, s), 3.03 (1H, m), 3.82 (2H, m), 3.87 (2H, s), 4.31 (2H, m); MS (FAB) m/z 1100, 1102 ([M+Na]$^+$), 1077 (M$^+$), 1061 ([M—H_2O])$^+$), 1046, 1048 ([M—OCH_3]$^+$), 1028, 1030 ([M—(OCH_3+H_2O)]$^+$), 1012 ([M—(OCH_3+2H_2O)]$^+$), 996 ([M-(2CH_3OH+OH)]$^+$), 980 ([M—(OCH_3+CH_3OH+2H_2O)]$^+$).

b) 4-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin

To a stirred, cooled (−45° C.) solution of 54 mg (0.05 mmol) of 40-O-(2-bromoacetoxy)ethyl-rapamycin in 0.5 mL of DMF is added a solution of 0.022 mL (0.25 mmol) of morpholine in 0.2 mL of DMF and the resulting mixture is sirred at that temperature for 1 h, then treated with aq. sodium bicarbonate. This mixnure is extracted three times with ethyl acetate. The organic solution is washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (95:5 ethyl acetate-methanol) yielding the title compound as an amorphous white solid: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.67 (3H, s), 1.76 (3H, s), 2.60 (3H, m), 3.07 (1H, m), 3.24 (2H, s), 3.78 (8H, m), 4.27 (2H, t); MS (FAB) m/z 1107 ([M+Na]$^+$), 1085 ([M+H]$^+$), 1067 ([M—OH]$^+$), 1053 ([M—OCH_3]$^+$), 1035 ([M—(OCH_3+H_2O)]$^+$).

MBA (rel. IC50)	1.3
IL-6 dep. prol. (rel. IC50)	4
MLR (rel. IC50)	3.5

Example 17

40-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin

The same procedure as described in example 16, step b) using imidazole affords the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.67 (3H, s), 1.78 (3H, s), 3.06 (1H, m), 3.80 (2H, m), 4.32 (2H, m), 4.73 (2H, s), 6.97 (1H, dd), 7.09 (1H, dd), 7.52 (1H, dd); MS (FAB) m/z 1066 ([M+H]$^+$), 1048 ([M—OH]$^+$), 1034 ([M—OCH_3]$^+$), 1016 ([M—(OCH_3+H_2O)]$^+$).
MBA (rel. IC50)

IL-6 dep. prol. (rel. IC50)	7.6
MLR (rel. IC50)	3.4

Example 18

40-O-[2-(N'-Methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin

The same procedure as described in example 16, step b) using N-methylpiperazine affords the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.67 (3H, s), 1.77 (3H, s), 2.78 (4H, s and m), 3.02 (4H, bs), 3.08 (1H, m), 3.32 (2H, s), 3.80 (2H, dd), 4.27 (2H, t); MS (FAB) m/z 1098 ([M+H]$^+$), 1066 ([M—OCH_3]$^+$).

MBA (rel. IC50)	2.6
IL-6 dep. prol. (rel. IC50)	10.3
MLR (rel. IC50)	5

Example 19

39-O-Desmethyl-39,40-O-ethylene-rapamycin

To a stirred, cooled (−20° C.) solution of 48 mg (0.05 mol) of 40-O-hydroxyethyl-rapamycin and 0.023 mL (0.20 mmol) of 2,6-lutidine in 0.5 mL of methylene chloride is added 0.008 mL (0.05 mmol) of triflic anhydride. The mixture is stirred at this temperature for 2 h. then allowed to warm to room temperature and stirred for one more hour. The reaction is quenched with aq. sodium bicarbonate and the resulting mixture is extracted with three portions of ethyl acetate. The organic solution is washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (30:70 hexane-ethyl acetate) to afford the title compound

as a white solid: ^{1}H NMR ($CDCl_3$) δ1.66 (3H, s), 1.75 (3H, s), 3.14 (3H, s), 3.35 (3H, s), 3.76 (4H, s); MS (FAB) m/z 948 ([M+Na]$^+$), 925 (M$^+$), 908 ([M—OH]$^+$), 894 ([M—OCH_3]$^+$), 876 ([M—(OCH_3+H_2O)]$^+$), 858 ([M—(OCH_3+2H_2O)]$^+$), 844 ([M-(2CH_3OH+OH)]$^+$), 826 ([M—(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	1.6
IL-6 dep. prol. (rel. IC50)	22.9
MLR (rel. IC50)	16

Example 20

(26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin

a) (26R)-26-Dihydro40-O-[2-(t-Butyldimethylsilyloxy)] ethyl-rapamycin

In 4.5 mL of 2:1 acetonitrile-acetic acid is dissolved 315 mg (1.2 mmol) of tetramethylamnonium-triacetoxyborohydride. The resulting solution is stirred for 1 h at room temperature and cooled to −35° C., then 161 mg (0.15 mmol) of 40-O-[2-(t-butyldimethylsilyl)oxy]ethyl-rapamycin is added. The resulting mixture is stirred at the same temperature overnight and is quenched by the addition of aq. sodium bicarbonate. The mixture is extracted with three portions of ethyl acetate. The organic solution is washed with aq. sodium bicarbonate, two portions of 30% aq. Rochelle's salt and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (40:60 hexane-ethyl acetate) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.06 (6H, s), 0.73 (1H, dd), 0.90 (9H, s), 1.64 (3H, s), 1.67 (3H, s), 3.02 (1H, m), 3.15 (1H, m), 3.64 (3H, m), 3.71 (2H, dd), 3.91 (1H, s); MS (FAB) m/z 1096 ([M+Na]$^+$), 1041 ([M—$HOCH_3$]$^+$), 1024 ([M—(OCH_3+H_2O)]$^+$), 1006 ([M—(OCH_3+2H_2O)]$^+$), 974 ([M—(OCH_3+CH_3OH+2H_2O)]$^+$).

b) (26R)-26-Dihydro40-O-(2-hydroxy)ethyl-rapamycin

Treatment of the compound obtained in step a) in the conditions described in example 8. step b) yields the title compound: ^{1}H NMR ($CDCl_3$) δ0.75 (1H, dd), 1.66 (3H, s), 1.70 (3H, s), 3.18 (1H, m), 3.52–3.84 (7H, m); MS (FAB) m/z 982 ([M+Na]$^+$), 928 ([M—OCH_3]$^+$), 910 ([M—(OCH_3+H_2O)]$^+$), 892 ([M—(OCH_3+2H_2O)]$^+$).

MBA (rel. IC50)	3.9
IL-6 dep. prol. (rel. IC50)	53
MLR (rel. IC50)	18

Example 21

28.0-O-Methyl-rapamycin

To a stirred solution of 103 mg (0.1 mmol) of 40-O-TBS-rapamycin (obtained by silylation of rapamycin with 1 eq. of TBS triflate in methylene chloride in the presence of 2 eq. of 2,6-lutidine at 0° C.) in 0.5 mL of methylene chloride is added 85.8 mg (0.40 mmol) of proton sponge followed by 44 mg (0.30 mmol) of trimethyloxonium tetrafluoroborate. The resulting brown heterogeneous mixture is stirred overnight, quenched with aq. sodium bicarbonate and extracted with ethyl acetate. The organic solution is washed with 1N HCl, aq. sodium bicarbonate and brine. then dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (60:40 hexane-ethyl acetate) to afford 40-O-t-butyldimethylsilyl-28-O-methyl-rapamycin. The latter compound is desilylated in the conditions described in example 10, step b) to afford, after PTLC (ethyl acetate), the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.70 (1H, dd), 1.68 (6H, 2s), 2.95 (1H, m), 3.13 (3H, s), 3.14 (3H, s), 3.28 (3H, s), 3.41 (3H, s); MS (FAB) m/z 950 ([M+Na]$^+$), 927 (M$^+$), 909 ([M—H_2O]$^+$), 896 ([M—OCH_3]$^+$), 878 ([M—(OCH_3+H_2O)]$^+$), 864 ([M—(OCH_3+CH_3OH)]$^+$), 846 ([M—(2CH_3OH+OH)]$^+$), 832 ([M—(OCH_3+2CH_3OH)]$^+$), 814 ([M-(3CH_3OH+OH)]$^+$).

MBA (rel. IC50)	1.58
IL-6 dep. prol. (rel. IC50)	1240
MLR (rel. IC50)	1300

Example 22

40-O-(2-aminoethyl)-rapamycin

a) 40-O-(2-bromoethyl)-rapamycin

A solution of 914 mg rapamycin in 5 mL toluene containing 0.64 ml of 2,6-lutidine and 1.28 g of 2-bromoethyl triflate is heated at 65 C for 18 h. The reaction mixture is then cooled to room temperature, poured on 20 ml of a saturated bicarbonate solution and extracted with 3×20 mL ethyl acetate. The organic phases are dried over sodium carbonate and the solvent removed at reduced pressure on the rotatory evaporator. The residue is chromatographed on 100 g silica gel, eluting with hexane/ethyl acetate 3/2 to afford 40-O-(2-bromoethyl)-rapamycin as an amorphous solid: MS (FAB) m/z 1044 and 1042 (100%; M+Na); 972 and 970 (55%, M—(MeOH+H2O)).

H-NMR (CDCl3) d: 0.72 (1H, q, J=12 Hz); 3.13 (3H, s); 3.33 (3H, s); 3.45 (3H,s); 3.9 (4H, m); 4.78 (1H, s)

b) 40-O-(2-azidoethyl)-rapamycin

A solution of 2.4 g of 40-O-(2-bromoethyl)-rapamycin in 40 mL DMF is treated with 0.19 g sodium azide at room temperature. After 2 h, the mixture is poured on 100 mL of saturated sodium bicarbonate and extracted with 3×100 mL ethyl acetate. The organic phases are combined, dried over sodium sulfate and the solvent removed under reduced pressure. The crude product is purified by chromatography on silica gel eluting with hexane/ethyl acetate to afford 40-O-(2-azidoethyl)-rapamycin: MS (FAB): 1005 (100%, M+Na); 951 (24%, M—MeOH); 933 (57%, M—(MeOH+H2O)

c) 40-O-(2-aminoethyl)-rapamycin

To a solution of 230 mg 40-O-(azidoethyl)-rapamycin in 3 mL of THF/water 5/1 at room temperature are added 307 mg of triphenylphosphine. The reaction mixture is becomes yellow. After 7 h, the reaction mixture is loaded on x g silical

gel and chromatographed with ethyl acetate/methanol/acetic acid 50/50/0.5 to afford the title product in the form of its acetate: MS (FAB) m/z 979 (45%, M+Na); 957 (100%, MH); 925 (63%, M—MeOH); 907 (25%, M—(MeOH+H2O)

MBA (rel. IC50): 0.7

IL-6 dep. prol. (rel. IC50): 10

Example 23

40-O-(2-acetaminoethyl)-rapamycin

To a solution of 101 mg of the acetate of 40-O-(2-aminoethyl)-rapamycin in 2 mL THF are added 0.02 mL pyridine and 0.07 mL acetyl chloride. The reaction mixture is kept at room temperature for 18 h and then poured on 7 mL saturated sodium bicarbonate. The aqueous phase is extracted 3 x with 5 mL ethyl acetate, the organic phases are combined and dried over sodium sulfate. The solvent is evaporated and the residue chromatographed on 10 g silica gel eluting first with ethyl acetate followed by ethyl acetatel/methanol/acetic acid 50/50/0.5 to afford the title product: MS (FAB) m/z 1021 (20%, M+Na); 967 (28%, M—MeOH); 949 (100%, M—(MeOH+H2O)

H-NMR (CDCl3) d: 071 (1H, q, J=12 Hz); 1.98 (3H, s); 3.13 (3H, s); 3.34 (3H, s); 3.44 (3H, s); 4.75 (1H, s)

MBA (rel. IC50): 1.1

IL-6 dep. prol. (rel. IC50): 2.3

Example 24

40-O-(2-nicotinanidoethyl)-rapamycin

101 mg of 40-(2-aminoethyl)-rapamycin acetate are dissolved in 5 ml ethyl acetate and extracted 2 x with saturated sodium bicarbonate. The organic phase is dried over sodium sulfate and the solvent evaporated. The residue is dissolved in 2 mL THF and treated with 22 mg DCC and 15 mg nicotinic acid. After 15 h at room temperature the reaction mixture is evaporated and the residue chromatographed on silica gel, eluting with ethyl acetate followed by ethyl acetate/methanol 9/1, to afford the title product: MS (FAB) m/z 1084 (80%, M+Na); 1062 (40%, MH); 1038 (100%, M—MeOH); 1012 (50%, M—(MeOH+H2O)

H-NMR (CDCl3) d: 0.72 (1H, q, J=12 Hz); 3.13 (3H, s); 3.33 (3H, s); 3.37 (3H, s); 7.39 (1H, dd; J=6 Hz, J=8 Hz), 8.19 (1H, d, J=8 Hz); 8.75 (1H, d, J=6 Hz); 9.04 (1H, broad s)

MBA (rel. IC50): 1.2

IL-6 dep. prol. (rel. IC50): 2.8

Example 25

40-O-(2-(N-Methyl-imidazo-2'-ylcarbethoxamido ethyl)-rapamycin

To a solution of 30 mg N-methyl-imidazol-2-carboxylic acid in 1 mL DMF are added 58 mg DCC and 58 mg HOBT. After 2 h, 150 mg 40-O-(2-aminoethyl)-rapamycin are added and the reaction mixture is stirred for 18 h at room temperature. The suspension is then filtered, the filtrate diluted with 5 mL ethyl acetate and washed with 2x2 mL of a saturated aqueous bicarbonate solution. The organic phase is dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue is chromatographed over 10 silica gel, eluting with hexane/ethyl acetate 1/4 and then ethyl acetate to afford the title product:

MS (FAB) m/z 1087 (36%, M+Na); 1065 (57%,MH); 1033 (100%, M—MeOH); 1015 (46%, M—(MeOH+H2O))

H-NMR (CDCl3) d: 0.72 (1H, q, J=12 Hz); 3.13 (3H, s); 3.33 (3H, s); 3.46 (3H, s) 4.03 (3H, s); 6.93 (1H, broad s); 6.98 (1H, broad s); 7.78 (1H, m)

MBA (rel. IC50): 1.1

IL-6 dep. prol. (rel. IC50): 7

Example 26

40-O-(2-ethoxycarbonylaminoethyl)-rapamycin

A solution of 200 mg 40-O-(2-azidoethyl)-rapamycin in 3 mL THF/water 5/1 is treated with 267 mg triphenylphosphine for 7 h at room temperature. Then 0.4 mL pyridine are added followed by 194 μL ethyl chloroformiate. After 2 h, the reaction mixture is poured on 5 mL ethyl acetate and washed successively with 10 mL saturated sodium bicarbonate, 5 mL water and 5 ml 10% citric acid. The organic phase is dried over sodium sulfate and the solvent evaporated. The residue is chromatographed over 20 g silica gel, eluting with ethyl acetate followed by ethyl acetate/methanol 9/1, to afford the title product: MS (FAB) m/z 1051 (35%, M+Na); 997 (30%, M—MeOH); 979 (100%, M—(MeOH+H2O)

H-NMR (CDCl3) d: 0.71 (1H, q, J=12 Hz); 1.24 (3H, t, J=8 Hz); 3.13 (3H, s); 3.34 (3H, s); 3.43 (3H, s); 4.10 (2H, q, J=8 Hz); 5.48 (1H, m)

MBA (rel. IC50): 1.1

IL-6 dep, prol. (rel. IC50): 1.7

Example 27

40-O-(2-tolylsulfonamidoethyl)-rapamycin

A solution of 200 mg 40-O-(2-aminoethyl)-rapamycin in 3 mL THF is treated with 0.4 mL pyridine and 390 mg tosyl chloride and the reaction mixture is stirred for 12 h at room temperature. The solution is then poured onto 5 ml of a saturated bicarbonate solution and the aqueous phase is extracted with 2x5 mL ethyl acetate. The combined organic phases are washed with 5 mL of 10% citric acid and 5 mL water. After drying on sodium sulfate the solvent is evaporated and the residue chromatographed on 20 g silica gel, eluting with hexane/ethyl acetate 1/1 to afford the title product as a white foam: MS (FAB) m/z 1133 (100%, M+Na); 1078 (25%, M—MeOH); 1061 (85%, M—(MeOH+H2O))

H-NMR (CDCL3) d: 0.68 (1H, q, J=12 Hz); 2.43 (3H, s); 3.13 (3H, s); 3.35 (3H, s); 3.41 (3H, s); 4.76 (1H, s); 5.85 (1H, t, J=6 Hz); 7.30 (2H, d, J=8 Hz); 7.75 (2H, d, J=8 Hz).

MBA (rel. IC50): 15.9

IL-6 dep. prol. (rel. IC50): 14

Example 28

40-O-[2-(4',5'-dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin

98 mg of 40-O-(2-azidoethyl)-rapamycin and 32 mg diethylacetylene dicarboxylate are suspended in 0.5 ml

toluene and heated at 65 C. for 5 h. The reaction mixture is then cooled at room temperature, loaded on 10 g silica gel and eluted with hexane/ethyl acetate 1/1 to afford the title product: MS (FAB) m/z 1175 (20%,M+Na); 1121 (15%, M—MeOH); 1103 (60%, M—(MeOH+H2O))

H-NMR (CDCl3) d: 0.62 (1H, q, J=12 Hz); 1.40 (3H, t, J=8 Hz); 1.42 (3H, t, J=8 Hz); 3.13 (3H, s); 3.25 (3H, s); 3.33 (3H, s)

MBA (rel. IC50): 2.7

IL-6 dep. prol. (rel. IC50): 12

The previous examples may also be made using as starting material instead of rapamycin, 9-deoxo-rapamycin, 26-dihydro rapamycin, or 9-deoxo-, 26-dihydro-rapamycin. Alternatively, and preferably, as described e.g., in example 20, the rapamycin compounds of the above examples may be hydrogenated or reduced, using suitable protecting groups where necessary. The following novel methods for reducing the keto at C9, or hydrogenating the keto at C26 are provided:

Example 29

Removal of keto at C9

A stream of hydrogen sulfide is passed at room temperature through a stirred solution of 3.2 g (3.5 mmol) of rapamycin in 50 ml pyridine and 2.5 ml DMF. The solution turns from colorless to yellow. After two hours, the introduction of hydrogen sulfide is stopped and stirring is continued for five days, during which time the solution turns gradually orange. TLC and HPLC analysis verifies complete consumption of the starting material and the presence of a single new compound. The solution is purged with nitrogen for one hour and concentrated under reduced pressure. The residue is taken up in ethyl acetate, washed with cold 1N HCl solution (3×), saturated sodium bicarbonate solution and saturated brine. The organic layer is dried over anhydrous sodium sulfate and filtered and concentrated under reduced pressure. The residue is taken up in ether and the precipitated sulfur is filtered off. Concentration of the ethereal solution followed by column chromatography on silica gel (10:4:1 CH_2Cl_2/i-Pr_2O/MeOH) yields 9-deoxorapamycin as a colorless foam. The identity of the product is confirmed by nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), and/or infrared spectrosopy (IR). 9-deoxorapamycin is found to exhibit the following characteristic physical data: ^{1}H NMR ($CDCL_3$) δ1.61 (3H,d,J=1 Hz, C17-CH_3), 1.76 (3H,d,J=1.2 Hz,C29-CH_3), 2.42 (1H,d,J=14.5 Hz, H-9), 2.74 (1H,d,J=14.5 Hz, H-9), 3.13 (3H,s,C16-OCH_3), 3.5 (3H,s,C27-OCH_3), 3.40 (3H,s,C39-OCH_3), 5.40 (1H,d,J=10 Hz, H-30), 5.57 (1H, dd,J=8.6 Hz, J_2=15 Hz, H-22), 5.96 (1H,d,J=9 Hz, H-18), 6.09 (1H,d,J=1.7 Hz, 10-OH), 6.15 (1H,dd,J_1=10 Hz, J_2=15 Hz, H-21), 6.37 (1H,dd,J_1=1.5 Hz, J_2=5 Hz, H-19), 6.38 (1H,J=9.5 Hz, H-20).

^{13}C NMR ($CDCl_3$) δ38.5 (C-9), 98.0 (C-10), 170.7 (C-1), 173.0 (C-8), 208.8 (C-32), 216.9 (C-26).

MS(FAB) m/z 922 8[M+Na^+]), 899 (M^+), 881 ([M—H_2O]$^+$), 868 ([M—OCH_3]$^+$), 850 ([M—(H_2O+OCH_3)]$^+$).

IR (major peaks)(cm^{-1}) 987, 1086, 1193, 1453, 1616, 1717, 1739, 3443.

MBA (rel. IC_{50}): 1

MLR (rel. IC_{50}): 14

IL-6 dep. prol. (rel. IC_{50}): 9

Example 30

Dihydrogenation of keto at C26

To a stirred solution of 421 mg (1.6 mmol) of tetramethylammonium triacetoxyborohydride in 2 ml of acetonitrile is added 2 ml of acetic acid. The resulting mixture is stirred for 30 minutes at room temperature and cooled to −35° C. At this temperature a solution of 180 mg (0.2 mmol) of 9-deoxo-rapamycin 1 ml of acetonitrile is added and the resulting mixture is allowed to stir for 24 hours. The mixture is quenched with a saturated sodium potassium tartrate solution and allowed to warm to room temperaure. Stirring is continued until both layers are clear and ethyl acetate is added. The layers are separated and the aqueous layer is extracted twice with ethyl acetate. The resulting organic solution is washed once with a 10% sodium bicarbonate solution and twice with saturated brine, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel (90:10 AcOEt-hexane). As the starting material in this case was 9-deoxorapamycin, the final compound is 9-deoxorapamycin, 26-dihydrorapamycin is produced as a colorless foam, having the following characteristic spectroscopic data: ^{1}H NMR ($CDCl_3$) (major isomer) δ0.9 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 0.93 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 1.00 (3H,d,J=6.9 Hz CH$\underline{CH_3}$), 1.07 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 1.17 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 1.61 (3H,d,J=1 Hz, C17-CH_3), 1.73 (3H,d,J=1.2 Hz, C29-CH_3), 2.43 (1H,dd,J=4.1 and 16.0 Hz, H-33), 2.46 (1H,d,J=13.8 Hz, H-9), 2.58 (1H,m,H-25), 2.77 (1H,d,J=13.8 Hz, H-9), 2.82 (1H,dd,J=8.3 and 16.0 Hz, H-33), 3.17 (1H,dd,J=4.1 and 9.2 Hz, H-27), 3.61 (2H,m, H-14 and H28), 5.19 (1H,ddd,J=4.1, 4.6 and 8.3 Hz, H-34), 5.49 (1H, broad d,J=5.0 Hz, H-2), 5.56 (1H,d,J=9.1 Hz, H-30), 5.75 (1H,dd, J=6.9 and 14.7 Hz, H-22), 5.76 (1H,s,10-OH), 5.99 (1H, broad d,J=9.2 Hz, H-18), 6.10 (1H,m,H-21), 6.36 (2H,m, H19 and H-20);

MS (FAB) m/z 924 ([M+Na]), 852 ([M—(H_2O+CH_3O)]$^+$).

MBA (rel. IC_{50}): 47

MLR (rel. IC_{50}): 134

IL-6 dep. prol. (rel. IC_{50}): 78

26-dihydrorapamycin is prepared in the same manner, using rapamycin in place of 9-deoxorapamycin. This product has the following characteristic spectroscopic data:

^{13}C-NMR ($CDCl_3$) (major isomer) d=208.3 (C-32); 194.0 (C-9); 169.3 (C-1); 166.6 (C-8); 140.9 (C-22); 136.5 (C-29); 136.2 (C-17); 133.5 (C-20); 129.1 (C-21); 128.7 (C-18); 126.2 (C-30); 125.3 (C-19); 98.6 (C-10); 84.4 (C-39); 83.9 (C-16; 81.6 (C-27); 75.4 (C-34); 74.3 (C-28); 73.9 (C-40); 72.9 (C-26); 67.4 (C-14); 59.1 (27-O$\underline{CH_3}$); 56.6 (39-O$\underline{CH_3}$); 5.59 (16-O$\underline{CH_3}$); 51.3 (C-2); 46.8 (C-31); 44.3 (C-6); 40.4 (C-33); 40.4 (C-25); 39.5 (C-24); 38.8 (C-15); 38.0 (C-36); 34.3 (C-23); 34.2 (C-38); 33.5 (C-11); 33.3 (C-37); 33.2 (C-35); 31.5 (C-42): 31.3 (C-41); 30.9 (C-13); 27.1 (C-12); 27.0 (C-3); 25.2 (C-5); 21.4 (23-$\underline{CH_3}$); 20.7 (C-4): 17.3 (31-

$\underline{C}H_3$); 16.1 (31-$\underline{C}$H3); 15.9 (35-$\underline{C}H_3$); 14.4 (25-$\underline{C}H_3$); 14.2 (29-$\underline{C}H_3$); 10.3 (17-$\underline{C}H_3$).

MS (FAB) m/z: 884 (M—OCH_3, 35%); 866 (M—[OCH_3+H_2O], 100%; 848 (M—[OCH_3+2H_2O], 40%).

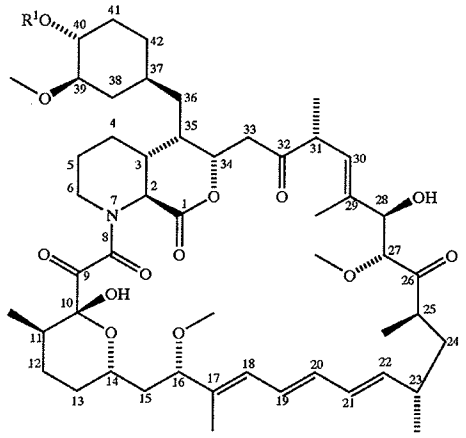
MBA (rel. IC_{50}): 1.7

MLR (rel. IC_{50}): 1

IL-6 dep. prol. (rel. IC_{50}): 7.5

What is claimed is:

1. A method for treating or preventing graft versus host disease or for treating an autoimmune disease selected from the group consisting of arthritis, rheumatic diseases, autoimmune hematological disorders, systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease, endocrine ophthalmopathy, Grave's disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes, anterior uveitis, posterior uveitis, keratoconjunctivitis sicca, vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis (with and without nephrotic syndrome), and juvenile dermatomyostis comprising administering to a person in need thereof an effective amount of a compound of the formula



wherein R^1 is hydroxy(C_{1-6})alkyl or hydroxy(C_{1-3})alkoxy(C_{1-3})alkyl.

2. A method of claim **1** wherein R^1 is hydroxy(C_{1-3})alkyl or hydroxy(C_{1-3})alkoxy(C_{1-3})alkyl.

3. A method of claim **1** wherein R^1 is hydroxy(C_{1-3})alkyl.

4. A method of claim **1** wherein R^1 is hydroxy(C_{1-3})alkoxy(C_{1-3})alkyl.

5. A method of claim **1** wherein the compound is 40-O-(3-hydroxypropyl)-rapamycin.

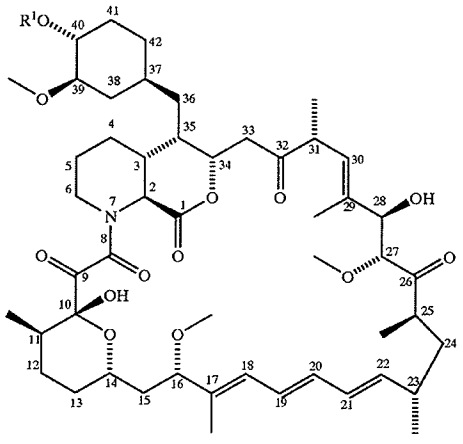
6. A method of claim **1** wherein the compound is 40-O-[2-(2-hydroxyethoxy)ethyl]-rapamycin.

7. A method of claim **1** wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, arthritis chronica progrediente, arthritis deformans, hemolytic anaemia, aplastic anaemia, pure red cell anaemia, idiopathic thrombocytopenia, ulcerative colitis, Crohn's disease, idiopathic nephrotic syndrome, and minimal change nephropathy.

8. A method for treating or preventing graft versus host disease or for treating an autoimmune disease selected from the group consisting of arthritis, rheumatic diseases, autoimmune hematological disorders, systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease, endocrine ophthalmopathy, Grave's disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes, anterior uveitis, posterior uveitis, keratoconjunctivitis sicca, vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis (with and without nephrotic syndrome), and juvenile dermatomyostis comprising administering to a person in need thereof an effective amount of 40-O-(2-hydroxyethyl)-rapamycin.

9. A method of claim **8** wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, arthritis chronica progrediente, arthritis deformans, hemolytic anaemia, aplastic anaemia, pure red cell anaemia, idiopathic thrombocytopenia, ulcerative colitis, Crohn's disease, idiopathic nephrotic syndrome, and minimal change nephropathy.

10. A method for treating or preventing the rejection of a transplanted organ or graft versus host disease or for treating an autoimmune disease selected from the group consisting of arthritis, rheumatic diseases, autoimmune hematological disorders, systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease, endocrine ophthalmopathy, Grave's disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes, anterior uveitis, posterior uveitis, keratoconjunctivitis sicca, vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis (with and without nephrotic syndrome), and juvenile dermatomyostis comprising administering to a host in need thereof an effective amount of a first compound of the formula



wherein R^1 is hydroxy(C_{1-6})alkyl or hydroxy(C_{1-3})alkoxy(C_{1-3})alkyl

and a second compound which is Ciclosporin, FK-506, an immunosuppressive derivative of Ciclosporin or FK-506, a corticosteroid, azathioprene, an immunosuppressive monoclonal antibody, an antiviral, or an antibiotic.

11. A method of claim 10 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is Ciclosporin.

12. A method of claim 10 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is FK-506.

13. A method of claim 10 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is an immunosuppressive derivative of Ciclosporin or FK-506.

14. A method of claim 10 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is a corticosteroid.

15. A method of claim 10 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is azathioprene.

16. A method of claim 10 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is an immunosuppressive monoclonal antibody.

17. A method of claim 16 wherein the second compound is an antibody to CD25.

18. A method of claim 16 wherein the second compound is an antibody to CD3.

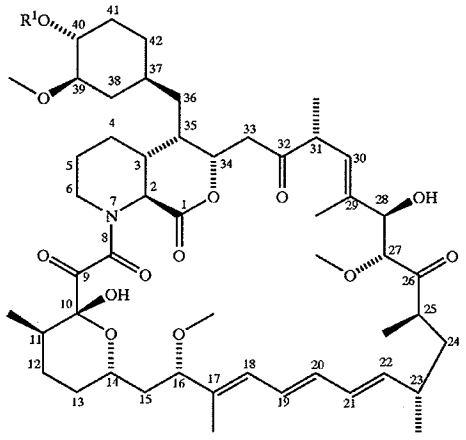
19. A method of claim 16 wherein the second compound is an antibody to CD45.

20. A method of claim 10 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is an antiviral.

21. A method of claim 10 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is an antibiotic.

22. A method of claim 10 wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, arthritis chronica progrediente, arthritis deformans, hemolytic anaemia, aplastic anaemia, pure red cell anaemia, idiopathic thrombocytopenia, ulcerative colitis, Crohn's disease, idiopathic nephrotic syndrome, and minimal change nephropathy.

23. A pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula

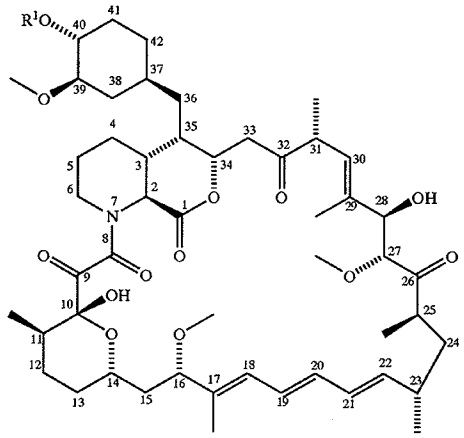


wherein R^1 is hydroxy(C_{1-3})alkyl
and a pharmaceutically acceptable carrier therefor.

24. A composition of claim 23 wherein the compound is 40-O-(3-hydroxypropyl)-rapamycin.

25. A pharmaceutical composition comprising a therapeutically effective amount of 40-O-(2-hydroxyethyl)-rapamycin and a pharmaceutically acceptable carrier therefor.

26. A pharmaceutical composition comprising a therapeutically effective amount of a first compound which is of the formula



wherein R^1 is hydroxy(C_{1-6})alkyl or hydroxy(C_{1-3})alkoxy (C_{1-3})alkyl
and a second compound which is Ciclosporin, FK-506, an immunosuppressive derivative of Ciclosporin or FK-506, a corticosteroid, azathioprene, an immunosuppressive monoclonal antibody, an antiviral, or an antibiotic, and a pharmaceutically acceptable carrier therefor.

27. A composition of claim 26 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is Ciclosporin.

28. A composition of claim 26 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is FK-506.

29. A composition of claim 26 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is an immunosuppressive derivative of Ciclosporin or FK-506.

30. A composition of claim 26 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is a corticosteroid.

31. A composition of claim 26 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is azathioprene.

32. A composition of claim 26 wherein the first compound is 40-O-(2-hydroxyethyl)-rapamycin and the second compound is an immunosuppressive monoclonal antibody.

33. A composition of claim 32 wherein the second compound is an antibody to CD25.

34. A composition of claim 32 wherein the second compound is an antibody to CD3.

35. A composition of claim 32 wherein the second compound is an antibody to CD45.

* * * * *

US007217286B2

(12) **United States Patent**
Falotico et al.

(10) **Patent No.: US 7,217,286 B2**
(45) **Date of Patent: *May 15, 2007**

(54) **LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/467,035**

(22) Filed: **Aug. 24, 2006**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 10/951,385, filed on Sep. 28, 2004, which is a continuation of application No. 10/408,328, filed on Apr. 7, 2003, now Pat. No. 6,808,536, which is a continuation of application No. 09/874,117, filed on Jun. 4, 2001, now Pat. No. 6,585,764, which is a continuation of application No. 09/061,568, filed on Apr. 16, 1998, now Pat. No. 6,273,913.

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(51) **Int. Cl.**
A61F 2/06 (2006.01)

(52) **U.S. Cl.** **623/1.42**

(58) **Field of Classification Search** 623/1.45–1.48; 427/2.1–2.31
See application file for complete search history.

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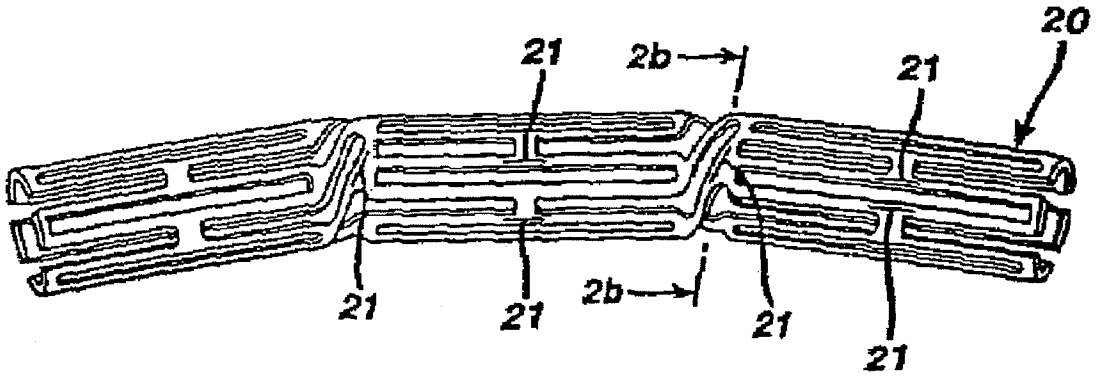
(57) **ABSTRACT**

Methods of preparing intravascular stents with a polymeric coating containing macrocyclic lactone (such as rapamycin or its analogs), stents and stent graphs with such coatings, and methods of treating a coronary artery with such devices. The macrocyclic lactone-based polymeric coating facilitates the performance of such devices in inhibiting restenosis.

5 Claims, 2 Drawing Sheets



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